INVENTOR SEARCH

=> d ibib abs ind l2 1

L2 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:1156499 HCAPLUS Full-text
DOCUMENT NUMBER: 142:49270
TITLE: Staurosporine derivatives for the treatment allergic and other conditions
INVENTOR(S): Coutre, Steven
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis Pharma GmbH
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004112794	A2	20041229	WO 2004-EP6562	20040617
WO 2004112794	A3	20050616		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004248909	A1	20041229	AU 2004-248909	20040617
AU 2004248909	B2	20080508		
CA 2527703	A1	20041229	CA 2004-2527703	20040617
EP 1638574	A2	20060329	EP 2004-740016	20040617
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
CN 1805749	A	20060719	CN 2004-80016821	20040617
BR 2004011563	A	20060801	BR 2004-11563	20040617
JP 2006527727	T	20061207	JP 2006-515982	20040617
CN 101164539	A	20080423	CN 2007-10165837	20040617
MX 2005013722	A	20060308	MX 2005-13722	20051215
IN 2005CN03427	A	20070727	IN 2005-CN3427	20051216
US 20070299049	A1	20071227	US 2007-560669	20070323
AU 2008201870	A1	20080522	AU 2008-201870	20080429

PRIORITY APPLN. INFO.:

US 2003-479575P	P	20030618
AU 2004-248909	A3	20040617
CN 2004-80016821	A3	20040617
WO 2004-EP6562	W	20040617

OTHER SOURCE(S): MARPAT 142:49270

AB The invention discloses the use of staurosporines derivs. for the curative, palliative or prophylactic treatment of allergic rhinitis, allergic dermatitis, drug allergy or food allergy, angioedema, urticaria, sudden infant death syndrome, bronchopulmonary aspergillosis, multiple sclerosis, or mastocytosis; as well as a method of treatment of warm-blooded animals in which a therapeutically ED of a staurosporine derivative is administered to a warm-blooded animal suffering from one of the above diseases or conditions. Compds. of the invention include e.g. midostaurin.

IC ICM A61K031-553
CC 1-12 (Pharmacology)
ST staurosporine deriv midostaurin allergic rhinitis dermatitis drug food allergy; sudden infant death syndrome bronchopulmonary aspergillosis staurosporine deriv midostaurin; angioedema urticaria multiple sclerosis mastocytosis staurosporine deriv midostaurin
IT Allergy
(allergic dermatitis; staurosporine derivs. for treatment allergic and other conditions)
IT Allergy
Inflammation
Nose, disease
(allergic rhinitis; staurosporine derivs. for treatment allergic and other conditions)
IT Dermatitis
(allergic; staurosporine derivs. for treatment allergic and other conditions)
IT Edema
(angioneurotic; staurosporine derivs. for treatment allergic and other conditions)
IT Mycosis
(aspergillosis, bronchopulmonary; staurosporine derivs. for treatment allergic and other conditions)
IT Respiratory system, disease
(bronchopulmonary aspergillosis; staurosporine derivs. for treatment allergic and other conditions)
IT Drug delivery systems
(capsules; staurosporine derivs. for treatment allergic and other conditions)
IT Drug delivery systems
(gels; staurosporine derivs. for treatment allergic and other conditions)
IT Drug delivery systems
(oral; staurosporine derivs. for treatment allergic and other conditions)
IT Allergy inhibitors
Antitumor agents
Canis familiaris
Drug allergy
Drug delivery systems
Food allergy
Human
Mastocytoma
Multiple sclerosis
Nervous system agents
Prophylaxis
Urticaria
(staurosporine derivs. for treatment allergic and other conditions)
IT c-Kit (protein)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(staurosporine derivs. for treatment allergic and other conditions)
IT Death
(sudden infant death syndrome; staurosporine derivs. for treatment allergic and other conditions)
IT Drug resistance
(to imatinib; staurosporine derivs. for treatment allergic and other conditions)
IT 152459-95-5, Imatinib
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(resistance to; staurosporine derivs. for treatment allergic and other conditions)

IT 138359-29-2, Kit tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(staurosporine derivs. for treatment allergic and other conditions)

IT 62996-74-1D, Staurosporine, derivs. 120685-11-2, Midostaurin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(staurosporine derivs. for treatment allergic and other conditions)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

RESULTS FROM SEARCHES IN REGISTRY, CAPLUS, MEDLINE, BIOSIS, EMBASE, AND DRUGU

```
=> d que stat l14
L4            1 SEA FILE=REGISTRY ABB=ON  MIDOSTAURIN/CN
L5          358 SEA FILE=HCAPLUS ABB=ON  L4 OR ?MIDOSTAURIN?
L6           15 SEA FILE=HCAPLUS ABB=ON  L5 AND (?MASTOCYTO? OR ?MAST?(W)?CELL?
                (W)?PROLIF?)
L7           47 SEA FILE=HCAPLUS ABB=ON  L5 AND ?CELL?(W)?PROLIF?
L8            2 SEA FILE=HCAPLUS ABB=ON  L7 AND (?MASTOCYTO?)
L9           15 SEA FILE=HCAPLUS ABB=ON  L6 OR L8
L10           1 SEA FILE=HCAPLUS ABB=ON  L9 AND (PRD<20030618 OR PD<20030618)
L11          19 SEA FILE=HCAPLUS ABB=ON  L7 AND (PRD<20030618 OR PD<20030618)
L12          20 SEA FILE=HCAPLUS ABB=ON  L10 OR L11
L13          50 SEA L12
L14          44 DUP REMOV L12 L13 (26 DUPLICATES REMOVED)


=> d ibib abs l14 1-44

L14  ANSWER 1 OF 44  HCAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2005:983764  HCAPLUS  Full-text
DOCUMENT NUMBER:          143:280575
TITLE:                    Post-transcriptional destabilization of PKCβII in
                          smooth muscle via glucose responsive instability
                          element, for use in detecting intracellular glucose
                          levels and human disease
INVENTOR(S):              Cooper, Denise R.; Patel, Niketa A.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 69 pp., Cont.-in-part of U.S.
                          Ser. No. 435,471.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ----------------    ----   --------    --------------------   --------
     US 20050197311       A1    20050908    US 2005-54024          20050208 <--
     US 6852529           B1    20050208    US 1999-435471         19991108
PRIORITY APPLN. INFO.:                      US 1999-435471      A2 19991108 <--
AB   The subject invention pertains to nucleic acid constructs for post-
     transcriptional control of expression of a polynucleotide encoding a protein
     in a cell, wherein the constructs include a metabolite responsive instability
     element such as the glucose-regulated mRNA instability element.  The subject
     invention further pertains to host cells and vectors comprising the nucleic
     acid constructs of the invention, as well as probes, methods, and kits for
     detecting metabolite responsive instability elements or mutations thereof.
     The present invention further concerns a reporter vector useful for detecting
     intracellular glucose and glucose-analogs, host cells genetically modified
     with the reporter vector, and methods for detecting intracellular glucose.
     The present invention utilizes an element that regulates mRNA (mRNA) stability
     in response to a metabolite such as glucose or a glucose analog.  This
     glucose-regulated mRNA instability element has been mapped to the protein
     kinase C βII (PKCβII) mRNA that was found to decrease in the presence of
     elevated glucose levels.  When cloned into a reporter vector, the region of
     PKCβII containing the mRNA instability element imparts glucose-sensitive
     instability to the mRNA that is transcribed, thereby down-regulating the
```

expression of the reporter gene when glucose is elevated. The reporter vector of the present invention may be introduced into host cells, allowing detection of intracellular glucose and glucose analogs within intact, living cells in real-time and, optionally, in a high-throughput format.

L14 ANSWER 2 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:696780 HCAPLUS Full-text
DOCUMENT NUMBER: 139:219397
TITLE: N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine coated stents
INVENTOR(S): Prescott, Margaret Forney; Feldman, David Louis
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003072159	A1	20030904	WO 2003-EP2028	20030227 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW				
RW: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR				
CA 2477558	A1	20030904	CA 2003-2477558	20030227 <--
AU 2003214079	A1	20030909	AU 2003-214079	20030227 <--
AU 2003214079	B2	20070531		
EP 1480688	A1	20041201	EP 2003-709729	20030227 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003008053	A	20041228	BR 2003-8053	20030227 <--
JP 2005519080	T	20050630	JP 2003-570902	20030227 <--
CN 1638823	A	20050713	CN 2003-804788	20030227 <--
CN 1326577	C	20070718		
NZ 534544	A	20070531	NZ 2003-534544	20030227 <--
RU 2341266	C2	20081220	RU 2004-129281	20030227 <--
IN 2004CN01878	A	20060623	IN 2004-CN1878	20040824 <--
MX 2004008361	A	20041126	MX 2004-8361	20040827 <--
NO 2004004093	A	20041124	NO 2004-4093	20040927 <--
US 20050209244	A1	20050922	US 2005-505398	20050429 <--
ZA 2004006191	A	20060531	ZA 2004-6191	20060317 <--
IN 2007CN04120	A	20080328	IN 2007-CN4120	20070919 <--
PRIORITY APPLN. INFO.:			US 2002-360254P P	20020228 <--
			WO 2003-EP2028 W	20030227 <--
			IN 2004-CN1878 A3	20040824

AB The invention relates to the local administration of N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3- pyridyl)-2-pyrimidine-amine (I) or a pharmaceutically acceptable salt or crystal form thereof, optionally in conjunction with one or more other active ingredients, and a device adapted for such local administration. I significantly reduced neointimal lesion formation in rats at 28 days following balloon injury when administered at a dose of 0.2-3.5 mg/kg.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004008591 EMBASE Full-text
TITLE: Flt3 in Acute Myelogenous Leukemia: Biology, Prognosis, and Therapeutic Implications.
AUTHOR: Voutsadakis, Ioannis A., Dr. (correspondence)
CORPORATE SOURCE: Hematology Division, INSERM U487, Institut Gustave-Roussy, Villejuif, France. ivout-sadakis@yahoo.com
AUTHOR: Voutsadakis, Ioannis A., Dr. (correspondence)
CORPORATE SOURCE: 121 Ippokratous Street, Athens 11472, Greece. ivout-sadakis@yahoo.com
AUTHOR: Voutsadakis, Ioannis A., Dr. (correspondence)
CORPORATE SOURCE: 121 Ippokratous Street, Athens 11472, Greece. ivout-sadakis@yahoo.com
SOURCE: Medical Oncology, (2003) Vol. 20, No. 4, pp. 311-323.
Refs: 100
ISSN: 1357-0560 CODEN: MONCEZ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
025 Hematology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jan 2004
Last Updated on STN: 16 Jan 2004

AB Flt3 is a tyrosine kinase receptor expressed on hematopoietic cells. Activating mutations of this receptor are encountered in over one-fourth of acute myelogenous leukemia (AML) cases and activate multiple intracellular pathways leading to cell proliferation, inhibition of apoptosis, and blockage of differentiation in leukemic blasts. AML with flt3 mutations has a worse prognosis than AML with normal flt3, at least in younger patients. Sevaral flt3 inhibitors are in various stages of preclinical and clinical development and it is hoped that specific therapies against AML with flt3 mutations will soon be available to the clinician.

L14 ANSWER 4 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003172212 EMBASE Full-text
TITLE: Tyrosine kinases as targets in cancer therapy - Successes and failures.
AUTHOR: Traxler, Peter, Dr. (correspondence)
CORPORATE SOURCE: Novartis Pharma AG, Oncology Research, CH-4002 Basel, Switzerland. peter.traxler@pharma.novartis.com
SOURCE: Expert Opinion on Therapeutic Targets, (Apr 2003) Vol. 7, No. 2, pp. 215-234.
Refs: 174
ISSN: 1472-8222 CODEN: EOTTAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 May 2003
Last Updated on STN: 19 May 2003

AB Protein kinases play a crucial role in signal transduction and also in cellular proliferation, differentiation and various regulatory mechanisms. The inhibition of growth-related kinases, especially tyrosine kinases, might therefore provide new therapies for diseases such as cancer. Due to the enormous progress that has been made in the past few years in the identification of the human genome, in molecular and cell biology technologies, in structural biology and in bioinformatics, the number of receptor and non-receptor tyrosine kinases that have been identified as valuable molecular targets has greatly increased. Currently, more than 20 different tyrosine kinase targets are under evaluation in drug discovery projects in oncology. The progress made in the crystallisation of protein kinases, in most cases complexed with ATP-site-directed inhibitors, has confirmed that the ATP-binding domain of tyrosine kinases is an attractive target for rational drug design; more than 20 ATP-competitive, low molecular weight inhibitors are in various phases of clinical evaluation. Meanwhile, clinical proof-of-concept (POC) has been achieved with several antibodies and small molecules targeted against tyrosine kinases. With Herceptin, Glivec and Iressa (registered in Japan), the first kinase drugs have entered the market. This review describes the preclinical and clinical status of low molecular weight drugs targeted against different tyrosine kinases (e.g., epidermal growth factor receptor [EGFR], vascular endothelial growth factor receptor [VEGFR], platelet-derived growth factor receptor [PDGFR], Kit, Fms-like tyrosine kinase [Flt]-3), briefly describes new targets, and provides a critical analysis of the current situation in the area of tyrosine kinase inhibitors.

L14 ANSWER 5 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:208879 HCAPLUS Full-text
DOCUMENT NUMBER: 140:245921
TITLE: The FIP1L1-PDGFRα kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia
AUTHOR(S): Cools, Jan; Stover, Elizabeth H.; Wlodarska, Iwona; Marynen, Peter; Gilliland, D. Gary
CORPORATE SOURCE: Division of Hematology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
SOURCE: Current Opinion in Hematology (2003), Volume Date 2004, 11(1), 51-57
CODEN: COHEF4; ISSN: 1065-6251
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Purpose of review: The idiopathic hypereosinophilic syndrome is a rare hematol. disorder characterized by sustained unexplained eosinophilia with associated end-organ damage and by a striking male predominance. The first insights into the mol. etiol. of this heterogeneous disease were obtained from a "bedside-to-bench" approach. Successful empiric treatment of patients with the hypereosinophilic syndrome with the selective tyrosine kinase inhibitor imatinib mesylate (Gleevec, Novartis) ultimately led to the discovery of the FIP1L1-PDGFRα fusion kinase in about half of the hypereosinophilic syndrome cases. Recent findings The FIP1L1-PDGFRA fusion gene is generated by a cryptic interstitial chromosomal deletion, del(4)(q12q12), which indicates that these cases are clonal hematopoietic malignancies and should be reclassified as chronic eosinophilic leukemias based on current World Health Organization recommendations. In addition, the FIP1L1-PDGFRA fusion gene was also identified in cases with systemic mast cell

disease. In vitro and in vivo studies confirmed that FIP1L1-PDGFRα is a therapeutic target of imatinib, forming a rational basis for the treatment of FIP1L1-PDGFRA pos. chronic eosinophilic leukemia and mastocytosis with imatinib. Similar to BCR-ABL-pos. leukemias, resistance to imatinib due to point mutations in the PDGFRα kinase domain may develop. We have explored strategies to circumvent resistance to imatinib using alternative tyrosine kinase inhibitors such as PKC412. Summary: The discovery of the FIP1L1-PDGFRA fusion gene in the hypereosinophilic syndrome is an example of the power of clin. translational research and identifies interstitial chromosomal deletion as a novel mechanism to generate oncogenic tyrosine kinase fusion genes.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003109698 EMBASE Full-text

TITLE: Inhibiting cyclin-dependent kinase/cyclin activity for the treatment of cancer and cardiovascular disease.

AUTHOR: Ivorra, C.; Samyn, H.; Edo, M.D.; Castro, C.; Sanz-Gonzalez, S.M.; Diez-Juan, A.; Andres, V. (correspondence)

CORPORATE SOURCE: Laboratory of Vascular Biology, Dept. Mole./Cellular Pathol. Ther., Inst. de Biomedicina de Valencia, C/ Jaime Roig 11, 46010 Valencia, Spain. vandres@ibv.csic.es

AUTHOR: Andres, V. (correspondence)

CORPORATE SOURCE: Inst. de Biomedicina de Valencia, Laboratory of Vascular Biology, Dept. Mole./Cellular Pathol. Ther., C/ Jaime Roig 11, 46010 Valencia, Spain. vandres@ibv.csic.es

SOURCE: Current Pharmaceutical Biotechnology, (Feb 2003) Vol. 4, No. 1, pp. 21-37. Refs: 230
ISSN: 1389-2010 CODEN: CPBUBP

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; General Review; (Review)

FILE SEGMENT: 016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 27 Mar 2003
Last Updated on STN: 27 Mar 2003

AB Excessive cell proliferation contributes to the pathobiology of human diseases with a high health and socioeconomic impact, including cancer and vascular occlusive diseases (e. g., atherosclerosis, in-stent restenosis, transplant vasculopathy, and vessel bypass graft failure). Recent advances in the understanding of the molecular networks governing the hyperplastic growth of tumors and vascular obstructive neointimal lesions have provided new perspectives for preventive and therapeutic strategies against these disorders. Mammalian cell proliferation requires the activation of several cyclin-dependent protein kinases (CDKs). Postranslational activation of CDKs is a complex process that involves their association with regulatory subunits called cyclins. The activity of CDK/cyclin holoenzymes is negatively regulated through their interaction with members of the CDK family of inhibitory proteins (CKIs). Moreover, over fifty low molecular weight pharmacological CDK inhibitors that target the ATP-binding pocket of the catalytic site of CDKs have been identified. In this review, we will discuss

the use of pharmacological and gene therapy strategies against CDK/cyclins in animal models and clinical trials of cancer and cardiovascular disease.

L14 ANSWER 7 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005426990 EMBASE Full-text
TITLE: Dissecting oncogenes and tyrosine kinases in AML cells.
AUTHOR: Bianchi, Elisabetta, Dr. (correspondence); Rogge, Lars
CORPORATE SOURCE: Laboratory of Immunoregulation, Department of Immunology, Institut Pasteur, Paris, France.
SOURCE: MedGenMed Medscape General Medicine, (2003) Vol. 5, No. 3.
Refs: 20
CODEN: MMGMCE
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
025 Hematology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Oct 2005
Last Updated on STN: 20 Oct 2005

L14 ANSWER 8 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003050314 EMBASE Full-text
TITLE: [Molecular target structures for the treatment of lung cancer].
Molekulare zielstrukturen fur die therapie des bronchialkarzinoms. Prinzip und erste klinische ergebnisse.
AUTHOR: Fischer, Berthold; Fischer, T.; Baumann, M.; Micke, P.; Buhl, R.; Pirker, R.
CORPORATE SOURCE: b.fischer@3-med.klinik.uni-mainz.de
SOURCE: Onkologe, (1 May 2002) Vol. 8, No. 5, pp. 494-501.
Refs: 33
ISSN: 0947-8965 CODEN: ONKOF4
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
037 Drug Literature Index
LANGUAGE: German
ENTRY DATE: Entered STN: 7 Feb 2003
Last Updated on STN: 7 Feb 2003

L14 ANSWER 9 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2002:457450 HCAPLUS Full-text
DOCUMENT NUMBER: 138:180272
TITLE: A protein kinase C inhibitor induces phenotypic reversion of ras-transformed pancreatic cancer cells and cooperatively blocks tumor cell proliferation with an anti-ras peptide
AUTHOR(S): Way, Denise; Smith, Steven; Sivendran, Sharmila; Chie, Lyndon; Kanovsky, Mecheal; Brandt-Rauf, Paul W.; Chung, Denise L.; Michl, Josef; Pincus, Matthew R.

CORPORATE SOURCE: Departments of Biology and Chemistry, Long Island University, Brooklyn, NY, 11201, USA
SOURCE: Cancer Chemotherapy and Pharmacology (2002), 49(6), 429-437
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have previously found that the staurosporine derivative, CGP 41 251, that has a high specificity for inhibiting protein kinase C (PKC), selectively blocks oncogenic ras-p21-induced oocyte maturation and that PKC and jun-N-terminal kinase (JNK), with which oncogenic ras-p21 directly interacts, reciprocally require each other's activation. We sought to determine whether CGP 41 251 blocks proliferation of ras-transformed mammalian cells and whether it synergistically exerts this effect with a ras-p21 peptide (residues 96-110) that interferes with the interaction of ras-p21 with JNK. We incubated ras-transformed rat pancreatic cancer TUC-3 cells and their normal counterpart pancreatic acinar BMRPA1 cells with CGP 42 251 alone and in the presence of the ras-p21 96-110 peptide, both in pre- and post-monolayer phases and determined cell counts and morphol. and, for TUC-3 cells, their ability to grow on soft agar. In the post-monolayer expts., we also evaluated these parameters after withdrawal of these agents. CGP 41 251, but not its inactive analog, CGP 42 700, blocked pre-monolayer growth and reduced post-monolayer cell counts of both TUC-3 and BMRPA1 cells (IC50 0.28 and 0.35 μM, resp.). After 2 wk of treatment, all the remaining TUC-3 cells exhibited the untransformed phenotype. Withdrawal of CGP 41 251 resulted in almost complete regrowth of the normal BMRPA1 cells while the reverted TUC-3 cells grew much more slowly. These effects were greatly enhanced by the presence of the ras-p21 96-110 peptide. CGP 41 251 strongly blocks growth of ras-transformed pancreatic cancer cells by causing cell death and by induction of phenotypic reversion. The enhancement of this effect by the ras-p21 96-110 peptide indicated synergy between it and CGP 41 251, allowing it to block proliferation of the transformed cells selectively. These findings suggest the possibility of using these two agents in anticancer therapy.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 10 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002211986 EMBASE Full-text
TITLE: Signaling inhibitors in the treatment of prostate cancer.
AUTHOR: Hudes, Gary R. (correspondence)
CORPORATE SOURCE: Department of Medical Oncology, Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111, United States .
SOURCE: Investigational New Drugs, (2002) Vol. 20, No. 2, pp. 159-173.
Refs: 120
ISSN: 0167-6997 CODEN: INNDDK
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 8 Jul 2002
Last Updated on STN: 8 Jul 2002

AB Inhibiting androgen receptor (AR) activation through medical or surgical castration and blockade of AR-androgen binding is the cornerstone of treatment for advanced prostate cancer. However, in most cases tumor growth eventually becomes androgen independent. Alternative mechanisms of AR activation, some of which involve growth factor receptor signaling, have been demonstrated in prostate cancer models, and it is likely that a number of autocrine and paracrine growth factor ligand-receptor interactions such as those of epidermal growth factors, fibroblast growth factors, and insulin-like growth factors contribute to the androgen independent phenotype by promoting cell proliferation and survival. Blocking activation and signaling through growth factor receptors and upstream signaling proteins has emerged as a credible approach to cancer treatment. Successful application of this approach in prostate cancer using a growing array of small molecule kinase inhibitors, antibodies, and antisense oligonucleotides will be greatly accelerated by elucidation of the key signaling pathways that maintain the androgen independent phenotype.

L14 ANSWER 11 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002067656 EMBASE Full-text
TITLE: Targeting protein kinase C: New therapeutic opportunities against high-grade malignant gliomas?.
AUTHOR: Da Rocha, A.B., Dr. (correspondence); Mans, D.R.A.; Regner, A.; Schwartsmann, G.
CORPORATE SOURCE: SOAD, Comprehensive Cancer Center, Lutheran University of Brazil, Rua Miguel Tostes 101, 92420-280 Canoas, RS, Brazil . brondani@terra.com.br
SOURCE: Oncologist, (2002) Vol. 7, No. 1, pp. 17-33.
Refs: 183
ISSN: 1083-7159 CODEN: OCOLF6
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 Mar 2002
Last Updated on STN: 7 Mar 2002

AB A large body of evidence suggests that the abnormal phenotype of neoplastic astrocytes, including their excessive proliferation rate and high propensity to invade surrounding tissues, results from mutations in critical genes involved in key cellular events. These genetic alterations can affect cell-surface-associated receptors, elements of signaling pathways, or components of the cell cycle clock, conferring a gain or a loss of relevant metabolic functions of the cells. The understanding of such phenomena may allow the development of more efficacious forms of cancer treatment. Examples are therapies specifically directed against overexpressed epidermal growth factor receptor, hyperactive Ras, excessively stimulated Raf-1, overproduced ornithine decarboxylase, or aberrantly activated cyclindependent kinases. The applicability of some of these approaches is now being assessed in patients suffering from primary malignant central nervous system tumors that are not amenable to current therapeutic modalities. Another potentially useful therapeutic strategy against such tumors involves the inhibition of hyperactive or overexpressed protein kinase C (PKC). This strategy is justified by the decrease in cell proliferation and invasion following inhibition of the activity of this enzyme observed in preclinical glioma models. Thus, interference with PKC activity may represent a novel form of experimental cancer treatment that may simultaneously restrain the

hyperproliferative state and the invasive capacity of high-grade malignant gliomas without inducing the expected toxicity of classical cytotoxic agents. Of note, the experimental use of PKC-inhibiting agents in patients with refractory high-grade malignant gliomas has indeed led to some clinical responses. The present paper reviews the current status of the biochemistry and molecular biology of PKC, as well as the possibilities for developing novel anti-PKC-based therapies for central nervous system malignancies.

L14 ANSWER 12 OF 44 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:356358 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300356358
TITLE: PKC412, an Oral FLT3 Inhibitor, Has Activity in Mutant FLT3 Acute Myeloid Leukemia (AML): A Phase II Clinical Trial.
AUTHOR(S): Stone, Richard M. [Reprint Author]; Klimek, Virginia [Reprint Author]; DeAngelo, Daniel J. [Reprint Author]; Nimer, Stephen [Reprint Author]; Estey, Eli [Reprint Author]; Galinsky, Ilene [Reprint Author]; Neuberg, Donna [Reprint Author]; Yap, Alan [Reprint Author]; Fox, Edward A. [Reprint Author]; Gilliland, D. G. [Reprint Author]; Griffin, James [Reprint Author]
CORPORATE SOURCE: Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 316. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 6 Aug 2003

AB Approximately 30% of AML patients have mutations in the FLT3 gene that result in constitutive activation of tyrosine kinase activity. The mutations are of two types: an internal tandem duplication (ITD) encoding an insertion of 3-33 amino acids within the juxtamembrane domain or a mutation in the activation loop codon D835. These activated FLT3 receptors induce spontaneous proliferation and prolonged viability in factor-dependent cell lines, and cause a lethal myeloproliferative syndrome (MPS) in mice. AML patients with mutated FLT3 tend to have a poor prognosis. A small molecule kinase inhibitor, PKC412 (N-benzylstaurosporine), was found to potently inhibit FLT3 kinase activity with an IC50 of < 10 nM, block FLT3-induced cell proliferation, and prolong the life of mice with FLT3-induced MPS. Since a tolerated and biologically active dose of PKC412 had been identified by phase I/II studies in patients with solid tumors, we conducted a phase II trial of PKC412 (75 mg po tid, continuously) in patients with AML whose blasts had either a FLT3 ITD or D835Y mutation. All patients had either relapsed or refractory disease or were not deemed candidates for myelosuppressive chemotherapy. Other eligibility criteria included ECOG performance status < 3, recovery from prior chemotherapy, and no treatment with hydroxyurea up to 7 days prior to study entry and thereafter. Of the initial eight (six male, median age 50, range 38-72) patients treated on this study, 3 had refractory AML (1-3 prior regimens) and 5 had relapsed AML (4 first relapse, CR duration 7-9 mo; 1 second relapse, CR1 of 22 months, CR 2 of 5 months). Five patients had normal cytogenetics. All had FLT3 ITD mutations (6-33 amino acids). The 8 patients received PKC412 for a median of 30 days (range 11-92 days). The

drug was well tolerated; grade 1 nausea, the most common side effect, occurred in most patients. Three patients discontinued drug for reasons other than disease progression: one on day 19 due to disease-or sepsis-related hyperbilirubinemia, one with baseline chronic renal failure (creatinine= 3.7 mg/dl), on day 11 due to shortness of breath who developed fatal pulmonary toxicity on day 18 from unknown causes, and one on day 25 due to severe lethargy who died on day 29 of unknown causes. Although difficult to determine in the setting of active AML, two patients may have had drug-induced neutropenia. Six patients experienced a significant transient reduction in the blood blast counts with maximum effect between days 8-42. One patient who had no blast reduction was the only patient who had no detectable wild type FLT3 allele. No CRs or PRs were noted although one patient's bone marrow blasts dropped from 80% pre-treatment to 30% on day 57; the peripheral blasts count decreased from 65,240/ul to 100/ul over the same interval. The decrease in blood blasts lasted 2.5 months. Western blot analysis on leukemic cells from this patient demonstrated constitutive tyrosine phosphorylation of FLT3 at initiation of therapy and absence of detectable FLT3 at 28 and 57 days post-therapy. We conclude that PKC412 has biological and clinical activity in AML apparently via inhibition of the FLT3 target. Further testing is warranted.

L14 ANSWER 13 OF 44 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:337291 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300337291
TITLE: FLT3 Receptors with Internal Tandem Duplications Signal through AKT/PKB and Forkhead (Foxo) Transcription Factors To Regulate Genes Controlling Cell Cycle Progression and Viability.
AUTHOR(S): Scheijen, Blanca [Reprint Author]; Ngo, Hai T. [Reprint Author]; Kang, Hyun [Reprint Author]; Griffin, James D. [Reprint Author]
CORPORATE SOURCE: Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp.
Abstract No. 232. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jul 2003
Last Updated on STN: 23 Jul 2003

AB In 27% of all acute myeloid leukemia (AML) cases and 37% of the patients with acute promyelocytic leukemia (APL), activating mutations of the FLT3 receptor have been identified, which frequently present as in-frame internal tandem duplications (ITD) at the juxtamembrane domain of the receptor. These findings implicate ITD-FLT3 mutations as the most common genetic alteration in AML. It has been shown that ITD-FLT3 receptors exhibit constitutive tyrosine kinase activity and activate signal transduction pathways in the absence of FLT3 ligand (FL) binding. Previous studies have also demonstrated that introduction of ITD-FLT3 into cytokine-dependent hematopoietic cell lines induces proliferation and prolonged viability. Furthermore, expression of ITD-FLT3 in murine bone marrow cells results in a lethal myeloproliferative syndrome. We have examined the signaling activities of ITD-FLT3 in more detail in an attempt to understand the critical pathways associated with cell transformation. To this end, the mutant receptor ITD4-FLT3

(FYVDFREYDEDFYVDFREY) was expressed in Ba/F3 cells under the control of a doxycycline-inducible promoter. We demonstrate that doxycycline-mediated induction of ITD4-FLT3 expression in interleukin-3 (IL-3)-deprived Ba/F3 cells is sufficient to promote cell proliferation and inhibit programmed cell death. Induction of ITD4-FLT3 protein levels is accompanied by activation-dependent phosphorylation of the serine/threonine kinase AKT/PKB, which can be blocked with tyrosine kinase inhibitor PKC412. The AKT/PKB pathway is known to play an important role in mediating cell survival in other cell systems, and Bad, MDM2, Caspase 9, GSK3beta and the Foxo subfamily of Forkhead transcription factors have been identified as possible substrates of AKT/PKB. Since there is strong genetic and biochemical evidence linking the Forkhead transcription factors to survival signaling, we examined in more detail whether ITD4-FLT3 may regulate the activity of Forkhead transcription factors Foxo1 (FKHR), Foxo3a (FKHRL1) and Foxo4 (AFX). In general, phosphorylation of Foxo proteins by AKT/PKB prohibits their nuclear localization and prevents transcriptional activation of target genes like Bim, FasL and p27Kip1. Our data show that induction of ITD4-FLT3 levels in Ba/F3 cells results in phosphorylation of Foxo3a, which is followed by downregulation of Bim and p27Kip1 expression in a PKC412-sensitive manner. In COS cells, ectopic expression of ITD4-FLT3 promotes shuttling of EGFP-Foxo1 protein from the nucleus into the cytoplasm, which requires the presence of conserved AKT phosphorylation sites in Foxo1. Addition of PI 3-kinase inhibitor LY294002 blocks ITD4-FLT3-induced relocalization of EGFP-Foxo1 to the cytoplasm. Furthermore, constitutive FLT3 kinase activity prohibits Foxo1 and Foxo4-mediated transcription activation in a reporter assay. These results indicate that oncogenic tyrosine kinases, like ITD-FLT3 receptors, can negatively regulate Forkhead transcription factors, thereby promoting cell survival through target genes like Bim and facilitate cell cycle progression by controlling expression of p27Kip1.

L14 ANSWER 14 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:703739 HCAPLUS Full-text
DOCUMENT NUMBER: 135:269653
TITLE: Use of multipotent neural stem cells and their progeny for the screening of drugs and other biological agents
INVENTOR(S): Weiss, Samuel; Reynolds, Brent; Hammang, Joseph P.; Baetge, E. Edward
PATENT ASSIGNEE(S): Neurospheres Holdings Ltd., Can.
SOURCE: U.S., 42 pp., Cont.-in-part of U.S. Ser. No. 385,404, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6294346	B1	20010925	US 1995-484406	19950607 <--
CA 2113118	A1	19930121	CA 1992-2113118	19920707 <--
CA 2113118	C	20020917		
WO 9301275	A1	19930121	WO 1992-CA283	19920707 <--
W: AU, CA, FI, JP, NO, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
AU 9222425	A	19930211	AU 1992-22425	19920707 <--
AU 665012	B2	19951214		
EP 594669	A1	19940504	EP 1992-914286	19920707 <--
EP 594669	B1	20030514		
EP 594669	B2	20071219		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				

JP 06509225 T 19941020 JP 1992-501862 19920707 <--
AT 240389 T 20030515 AT 1992-914286 19920707 <--
EP 1329499 A2 20030723 EP 2003-7791 19920707 <--
EP 1329499 A3 20030903
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC
ES 2198404 T3 20040201 ES 1992-914286 19920707 <--
CA 2147162 A1 19940428 CA 1993-2147162 19931015 <--
CA 2147162 C 20020430
WO 9409119 A1 19940428 WO 1993-CA428 19931015 <--
W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
AU 9351474 A 19940509 AU 1993-51474 19931015 <--
AU 683023 B2 19971030
EP 664832 A1 19950802 EP 1993-922482 19931015 <--
EP 664832 B1 20020724
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 08502172 T 19960312 JP 1994-509473 19931015 <--
AT 221117 T 20020815 AT 1993-922482 19931015 <--
ES 2180547 T3 20030216 ES 1993-922482 19931015 <--
CA 2148138 A1 19940511 CA 1993-2148138 19931027 <--
CA 2148138 C 20020108
WO 9410292 A1 19940511 WO 1993-CA456 19931027 <--
W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
AU 9453676 A 19940524 AU 1994-53676 19931027 <--
EP 669973 A1 19950906 EP 1993-923994 19931027 <--
EP 669973 B1 20030312
EP 669973 B2 20070418
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 08502652 T 19960326 JP 1994-510503 19931027 <--
AT 234353 T 20030315 AT 1993-923994 19931027 <--
EP 1298202 A2 20030402 EP 2002-18736 19931027 <--
EP 1298202 A3 20031203
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE
ES 2194016 T3 20031116 ES 1993-923994 19931027 <--
NO 9400056 A 19940303 NO 1994-56 19940106 <--
CA 2155024 A1 19940804 CA 1994-2155024 19940128 <--
CA 2155024 C 19991214
WO 9416718 A1 19940804 WO 1994-US1053 19940128 <--
W: AU, CA, FI, JP, KR, NO, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AU 9460983 A 19940815 AU 1994-60983 19940128 <--
AU 687785 B2 19980305
EP 681477 A1 19951115 EP 1994-907366 19940128 <--
EP 681477 B1 20040331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 08505762 T 19960625 JP 1994-510446 19940128 <--
JP 3583778 B2 20041104
AT 262912 T 20040415 AT 1994-907366 19940128 <--
ES 2218524 T3 20041116 ES 1994-907366 19940128 <--
CA 2175992 A1 19950518 CA 1994-2175992 19941108 <--
CA 2175992 C 20080401
WO 9513364 A1 19950518 WO 1994-CA614 19941108 <--
W: AU, CA, CN, FI, JP, NO, RU, US

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

AU	9480561	A	19950529	AU 1994-80561	19941108 <--
AU	697894	B2	19981022		
EP	728194	A1	19960828	EP 1994-931482	19941108 <--
EP	728194	B1	20030108		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE

CN	1141058	A	19970122	CN 1994-194785	19941108 <--
JP	09507747	T	19970812	JP 1995-513499	19941108 <--
JP	3952508	B2	20070801		
AT	230795	T	20030115	AT 1994-931482	19941108 <--
ES	2189807	T3	20030716	ES 1994-931482	19941108 <--
FI	9501677	A	19950407	FI 1995-1677	19950407 <--
NO	9501378	A	19950407	NO 1995-1378	19950407 <--
NO	324411	B1	20071008		
FI	9502022	A	19950427	FI 1995-2022	19950427 <--
NO	9501617	A	19950427	NO 1995-1617	19950427 <--
NO	324412	B1	20071008		
US	5750376	A	19980512	US 1995-483122	19950607 <--
US	5851832	A	19981222	US 1995-486648	19950607 <--
FI	9503569	A	19950925	FI 1995-3569	19950726 <--
NO	9502985	A	19950727	NO 1995-2985	19950727 <--
NO	322466	B1	20061009		
CN	1161744	A	19971008	CN 1995-195867	19950922 <--
EP	1130394	A1	20010905	EP 2001-101622	19950922 <--
EP	1130394	B1	20061115		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE

FI	9601855	A	19960604	FI 1996-1855	19960430 <--
NO	9601859	A	19960703	NO 1996-1859	19960508 <--
NO	317724	B1	20041213		
AU	9749241	A	19980312	AU 1997-49241	19971224 <--
AU	703729	B2	19990401		
US	20030082515	A1	20030501	US 2002-199189	20020719 <--
US	7101709	B2	20060905		
US	20030095956	A1	20030522	US 2002-199918	20020719 <--
US	7115418	B2	20061003		
US	20030109008	A1	20030612	US 2002-199830	20020719 <--
JP	2007014352	A	20070125	JP 2006-276639	20061010 <--

PRIORITY APPLN. INFO.:

US 1991-726812	B1	19910708	<--
US 1992-961813	B1	19921016	<--
US 1992-967622	B1	19921028	<--
US 1993-10829	B1	19930129	<--
US 1993-149508	B2	19931109	<--
US 1994-221655	B2	19940401	<--
US 1994-270412	B2	19940705	<--
US 1994-311099	B2	19940923	<--
US 1994-338730	B2	19941114	<--
US 1994-359945	B2	19941220	<--
US 1995-376062	B2	19950120	<--
US 1995-385404	B2	19950207	<--
EP 1992-914286	A3	19920707	<--
WO 1992-CA283	W	19920707	<--
WO 1993-CA428	W	19931015	<--
EP 1993-923994	A3	19931027	<--
JP 1994-510503	A3	19931027	<--
WO 1993-CA456	W	19931027	<--
WO 1994-US1053	W	19940128	<--
WO 1994-CA614	W	19941108	<--
US 1994-339730	B2	19941114	<--
US 1994-359345	A	19941220	<--
US 1995-481893	A	19950607	<--

US 1995-486313 A1 19950607 <--
EP 1995-931864 A3 19950922 <--
US 2002-726812 B1 20020719 <--

AB A culture method for determining the effect of a biol. agent on multipotent neural stem cell progeny is provided. In the presence of growth factors, multipotent neural stem cells are induced to proliferate in culture. The multipotent neural stem cells may be obtained from normal neural tissue or from a donor afflicted with a disease such as Alzheimer's Disease, Parkinson's Disease or Down's Syndrome. At various stages in the differentiation process of the multipotent neural stem cell progeny, the effects of a biol. agent, such as a virus, protein, peptide, amino acid, lipid, carbohydrate, nucleic acid or a drug or pro-drug on cell activity are determined Addnl., a method of screening the effects of biol. agents on a clonal population of neural cells is provided. The technol. provides an efficient method for the generation of large nos. of pre- and post-natal neural cells under controlled, defined conditions. The disclosed cultures provide an optimal source of normal and diseased neural cells at various developmental stages, which can be screened for potential side effects in addition to testing the action and efficacy of different biol. agents.

REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 15 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001377208 EMBASE Full-text
TITLE: Protein kinase C isozymes, novel phorbol ester receptors and cancer chemotherapy.
AUTHOR: Barry, O.P. (correspondence); Kazanietz, M.G.
CORPORATE SOURCE: Cork Cancer Research Center, Department of Medicine, Cork University Hospital, Wilton Road, Cork, Ireland. goggieie@yahoo.com
SOURCE: Current Pharmaceutical Design, (2001) Vol. 7, No. 17, pp. 1725-1744.
Refs: 188
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Nov 2001
Last Updated on STN: 15 Nov 2001

AB Recent years have seen extensive growth in the understanding of the role(s) of the various PKC isozymes and novel receptors for the phorbol ester tumor promoters. The PKC family of serine-threonine kinases is an important regulator of signaling cascades that control cell proliferation and death, and therefore represent targets for cancer therapy. While past interests have focused on PKC-selective inhibitors, more recently, intensive research has been underway for selective activators and inhibitors for each individual PKC isozyme. In the past few years a large number of PKC activators and inhibitors with potential as anticancer agents have been developed. A number of these compounds are already in Phase II clinical testing. As a new generation of cancer chemotherapeutic agents are designed, developed and put through a series of rigorous clinical trials, we can anticipate achieving exquisite control over PKC-mediated regulatory pathways, leading ultimately to a greater understanding of different cancers.

L14 ANSWER 16 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002234146 EMBASE Full-text
TITLE: Targeting protein kinases for tumor therapy.
AUTHOR: Sachsenmaier, Christoph, Dr. (correspondence)
CORPORATE SOURCE: KTB Tumorforschungsgesellschaft mbH, Klinik fur Tumorbiologie, Breisacher Strasse 117, D-79106 Freiburg, Germany. sachsenm@tumorbio.uni-freiburg.de
SOURCE: Onkologie, (2001) Vol. 24, No. 4, pp. 346-355.
Refs: 135
ISSN: 0378-584X CODEN: ONKOD2
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; German
ENTRY DATE: Entered STN: 11 Jul 2002
Last Updated on STN: 11 Jul 2002

AB Phosphorylation is the most common biochemical modification of cellular molecules, regulating fundamental cellular processes like growth, differentiation, proliferation, movement, and death. It is now clear that protein and lipid kinases as well as phosphatases are causally involved in human disease, especially in cancer. The first part of this review tries to compile our current knowledge about the involvement of protein kinases in human cancer. Phosphatases as well as phospholipid kinases will be omitted from this article for the purpose of simplification. In the second part an updated list of ongoing clinical trials involving protein kinases as targets for tumor therapy will be given, together with a brief summary of technical approaches in targeting protein kinases for therapy.

L14 ANSWER 17 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001191187 EMBASE Full-text
TITLE: Mitogenic signaling and the relationship to cell cycle regulation in astrocytomas.
AUTHOR: Yong, V. Wee (correspondence)
CORPORATE SOURCE: University of Calgary, 3330 Hospital Drive NW, Calgary, Alta. T2N 4N1, Canada. vyong@acs.ucalgary.ca
AUTHOR: Besson, Arnaud
SOURCE: Journal of Neuro-Oncology, (2001) Vol. 51, No. 3, pp. 245-264.
Refs: 148
ISSN: 0167-594X CODEN: JNODD2
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 008 Neurology and Neurosurgery
005 General Pathology and Pathological Anatomy
038 Adverse Reactions Titles
037 Drug Literature Index
030 Clinical and Experimental Pharmacology
029 Clinical and Experimental Biochemistry
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 14 Jun 2001
Last Updated on STN: 14 Jun 2001

AB The activity and regulation of a number of mitogenic signaling pathways is aberrant in astrocytomas, and this is thought to play a crucial role in the development of these tumors. The cascade of events leading to the formation and the progression from low-grade to high-grade astrocytomas is well characterized. These events include activating mutations, amplification, and overexpression of various growth factor receptors (e.g. epidermal growth factor receptor (EGFR), platelet derived growth factor receptor (PDGFR), c-Met), signaling intermediates (e.g. Ras and Protein kinase C (PKC)), and cell cycle regulatory molecules (e.g. mouse double minute-2 (Mdm2), cyclin-dependent kinase-4 (CDK4), and CDK6), that positively regulate proliferation and cell cycle progression. Inactivating mutations and deletions of signaling and cell cycle regulatory molecules that negatively regulate proliferation and cell cycle progression (e.g. p53, p16/INK4a, p14/ARF, p15/INK4b, retinoblastoma protein (Rb), and Phosphatase and tensin homologue deleted from chromosome 10 (PTEN)) also participate actively in the development of the transformed phenotype. Several mitogenic pathways are also stimulated via an autocrine loop, with astrocytoma cells expressing both the receptors and the respective cognate ligand. Due to the multitude of factors involved in astrocytoma pathogenesis, attempts to target a single pathway have not given satisfactory results. The simultaneous targeting of several pathways or the targeting of signaling intermediates, such as Ras or PKC, situated downstream of many growth factor receptor signaling pathways may show more efficacy in astrocytoma therapy. We will give an overview of how the combination of these aberrations drive astrocytoma cells into a relentless proliferation and how these signaling molecules may constitute relevant therapeutic targets.

L14 ANSWER 18 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER:	2001386886 EMBASE Full-text
TITLE:	Anti-proliferative effects of new staurosporine derivatives isolated from a marine ascidian and its predatory flatworm.
AUTHOR:	Schupp, P. (correspondence)
CORPORATE SOURCE:	Center for Marine Biofouling and Bio-Innovation, University of New South Wales, Sydney 2052, Australia. p.schupp@unsw.edu.au
AUTHOR:	Steube, K.; Meyer, C.
CORPORATE SOURCE:	Deutsche Sammlung von Mikroorganismen, Zellkulturen GmbH, Mascheroder Weg 1b, D-38124 Braunschweig, Germany.
AUTHOR:	Proksch, P.
CORPORATE SOURCE:	Institut fur Pharmazeutische Biologie, Universitatsstrasse 1, 40225 Dusseldorf, Germany.
AUTHOR:	Schupp, P. (correspondence)
CORPORATE SOURCE:	Ctr. Mar. Biofouling/Bio-Innovation, University of New South Wales, Sydney, NSW 2052, Australia. p.schupp@unsw.edu.au
SOURCE:	Cancer Letters, (28 Dec 2001) Vol. 174, No. 2, pp. 165-172. Refs: 44 ISSN: 0304-3835 CODEN: CALEDQ
PUBLISHER IDENT.:	S 0304-3835(01)00694-2
COUNTRY:	Ireland
DOCUMENT TYPE:	Journal; Article
FILE SEGMENT:	016 Cancer 025 Hematology 030 Clinical and Experimental Pharmacology 037 Drug Literature Index
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 15 Nov 2001

Last Updated on STN: 15 Nov 2001

AB Nine indolocarbazole alkaloids of the staurosporine type, including three new derivatives, were evaluated for their potential as inhibitors of cell proliferation and macromolecule synthesis. Four derivatives were tested as inhibitors of cell proliferation with twelve human leukemia cell lines and demonstrated powerful antiproliferative activities, with 3-hydroxystaurosporine being the most potent. IC(50) values were determined using the cell line MONO-MAC-6 and with an IC(50) of 13 ng/ml, 3-hydroxystaurosporine turned out to be one of the most active staurosporine-type inhibitors described so far. All derivatives, except 3-hydroxy-3'-demethoxy-3'-hydroxystaurosporine and 4'-N-methylstaurosporine very strongly reduced RNA and DNA synthesis with 3-hydroxystaurosporine again being the strongest inhibitor. Analysis of structure-activity relationships demonstrated that hydroxylation of staurosporine at position 3 of the indolocarbazole moiety caused an increase in anti-proliferative activity, while hydroxylation at carbon 11 resulted in a decrease in activity. Our results suggest that not only the presence or absence of hydrophilic substitutions, but also the position of the alteration within the molecule, is important in the antiproliferative properties of the various staurosporine analogues. .COPYRGT. 2001 Elsevier Science Ireland Ltd. All rights reserved.

L14 ANSWER 19 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:378161 HCAPLUS Full-text
DOCUMENT NUMBER: 133:27162
TITLE: In vivo genetic modification of growth factor-responsive neural precursor cells
INVENTOR(S): Weiss, Samuel; Reynolds, Brent; Hammang, Joseph P.; Baetge, E. Edward
PATENT ASSIGNEE(S): NeuroSpheres Holdings Ltd., Can.
SOURCE: U.S., 42 pp., Cont.-in-part of U.S. Ser. No. 385,404, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6071889	A	20000606	US 1995-479795	19950607 <--
CA 2113118	A1	19930121	CA 1992-2113118	19920707 <--
CA 2113118	C	20020917		
WO 9301275	A1	19930121	WO 1992-CA283	19920707 <--
W: AU, CA, FI, JP, NO, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
AU 9222425	A	19930211	AU 1992-22425	19920707 <--
AU 665012	B2	19951214		
EP 594669	A1	19940504	EP 1992-914286	19920707 <--
EP 594669	B1	20030514		
EP 594669	B2	20071219		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
JP 06509225	T	19941020	JP 1992-501862	19920707 <--
AT 240389	T	20030515	AT 1992-914286	19920707 <--
EP 1329499	A2	20030723	EP 2003-7791	19920707 <--
EP 1329499	A3	20030903		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC				
ES 2198404	T3	20040201	ES 1992-914286	19920707 <--
CA 2147162	A1	19940428	CA 1993-2147162	19931015 <--
CA 2147162	C	20020430		

```
WO 9409119          A1    19940428    WO 1993-CA428          19931015 <--
    W:  AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP,
        KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD,
        SE, SK, UA, VN
    RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,
        BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
AU 9351474          A     19940509    AU 1993-51474          19931015 <--
AU 683023           B2    19971030
EP 664832           A1    19950802    EP 1993-922482         19931015 <--
EP 664832           B1    20020724
    R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 08502172         T     19960312    JP 1994-509473         19931015 <--
AT 221117           T     20020815    AT 1993-922482         19931015 <--
ES 2180547          T3    20030216    ES 1993-922482         19931015 <--
CA 2148138          A1    19940511    CA 1993-2148138        19931027 <--
CA 2148138          C     20020108
WO 9410292          A1    19940511    WO 1993-CA456          19931027 <--
    W:  AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP,
        KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD,
        SE, SK, UA, VN
    RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,
        BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
AU 9453676          A     19940524    AU 1994-53676          19931027 <--
EP 669973           A1    19950906    EP 1993-923994         19931027 <--
EP 669973           B1    20030312
EP 669973           B2    20070418
    R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 08502652         T     19960326    JP 1994-510503         19931027 <--
AT 234353           T     20030315    AT 1993-923994         19931027 <--
EP 1298202          A2    20030402    EP 2002-18736          19931027 <--
EP 1298202          A3    20031203
    R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE
ES 2194016          T3    20031116    ES 1993-923994         19931027 <--
NO 9400056          A     19940303    NO 1994-56             19940106 <--
CA 2155024          A1    19940804    CA 1994-2155024        19940128 <--
CA 2155024          C     19991214
WO 9416718          A1    19940804    WO 1994-US1053         19940128 <--
    W:  AU, CA, FI, JP, KR, NO, US
    RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AU 9460983          A     19940815    AU 1994-60983          19940128 <--
AU 687785           B2    19980305
EP 681477           A1    19951115    EP 1994-907366         19940128 <--
EP 681477           B1    20040331
    R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 08505762         T     19960625    JP 1994-510446         19940128 <--
JP 3583778          B2    20041104
AT 262912           T     20040415    AT 1994-907366         19940128 <--
ES 2218524          T3    20041116    ES 1994-907366         19940128 <--
CA 2175992          A1    19950518    CA 1994-2175992        19941108 <--
CA 2175992          C     20080401
WO 9513364          A1    19950518    WO 1994-CA614          19941108 <--
    W:  AU, CA, CN, FI, JP, NO, RU, US
    RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AU 9480561          A     19950529    AU 1994-80561          19941108 <--
AU 697894           B2    19981022
EP 728194           A1    19960828    EP 1994-931482         19941108 <--
EP 728194           B1    20030108
    R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
CN 1141058          A     19970122    CN 1994-194785         19941108 <--
JP 09507747         T     19970812    JP 1995-513499         19941108 <--
```

JP 3952508	B2	20070801			
AT 230795	T	20030115	AT 1994-931482	19941108	<--
ES 2189807	T3	20030716	ES 1994-931482	19941108	<--
FI 9501677	A	19950407	FI 1995-1677	19950407	<--
NO 9501378	A	19950407	NO 1995-1378	19950407	<--
NO 324411	B1	20071008			
FI 9502022	A	19950427	FI 1995-2022	19950427	<--
NO 9501617	A	19950427	NO 1995-1617	19950427	<--
NO 324412	B1	20071008			
US 5750376	A	19980512	US 1995-483122	19950607	<--
US 5851832	A	19981222	US 1995-486648	19950607	<--
FI 9503569	A	19950925	FI 1995-3569	19950726	<--
NO 9502985	A	19950727	NO 1995-2985	19950727	<--
NO 322466	B1	20061009			
CN 1161744	A	19971008	CN 1995-195867	19950922	<--
EP 1130394	A1	20010905	EP 2001-101622	19950922	<--
EP 1130394	B1	20061115			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE					
FI 9601855	A	19960604	FI 1996-1855	19960430	<--
NO 9601859	A	19960703	NO 1996-1859	19960508	<--
NO 317724	B1	20041213			
AU 9749241	A	19980312	AU 1997-49241	19971224	<--
AU 703729	B2	19990401			
US 20030082515	A1	20030501	US 2002-199189	20020719	<--
US 7101709	B2	20060905			
US 20030095956	A1	20030522	US 2002-199918	20020719	<--
US 7115418	B2	20061003			
US 20030109008	A1	20030612	US 2002-199830	20020719	<--
JP 2007014352	A	20070125	JP 2006-276639	20061010	<--
PRIORITY APPLN. INFO.:			US 1991-726812	A2 19910708	<--
			US 1992-961813	B1 19921016	<--
			US 1992-967622	B1 19921028	<--
			US 1993-10829	B1 19930129	<--
			US 1993-149508	B2 19931109	<--
			US 1994-221655	B1 19940401	<--
			US 1994-270412	B2 19940705	<--
			US 1994-311099	B2 19940923	<--
			US 1994-338730	B2 19941114	<--
			US 1994-359945	B2 19941220	<--
			US 1995-376062	B2 19950120	<--
			US 1995-385404	B2 19950207	<--
			EP 1992-914286	A3 19920707	<--
			WO 1992-CA283	W 19920707	<--
			WO 1993-CA428	W 19931015	<--
			EP 1993-923994	A3 19931027	<--
			JP 1994-510503	A3 19931027	<--
			WO 1993-CA456	W 19931027	<--
			WO 1994-US1053	W 19940128	<--
			WO 1994-CA614	W 19941108	<--
			US 1994-339730	B2 19941114	<--
			US 1994-359345	A 19941220	<--
			US 1995-481893	A 19950607	<--
			US 1995-486313	A1 19950607	<--
			EP 1995-931864	A3 19950922	<--
			US 2002-726812	B1 20020719	<--

AB Methods for administering genetic material to dividing neural precursor cell populations in vivo are provided. The genetic material may comprise useful genes for neurotransmitters, growth factors, growth factor receptors, and the like. The genetic material is administered to the brain with one or more growth factors. The growth factors induce proliferation of neural precursor

cells, thereby facilitating the incorporation of the genetic material into the cell progeny.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 20 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2000152771 EMBASE Full-text
TITLE: Staurosporine analogues - Pharmacological toys or useful antitumour agents?.
AUTHOR: Gescher, Andreas (correspondence)
CORPORATE SOURCE: Med. Res. Council Toxicology Unit, Ctr. Mechanisms Hum. Toxicity, U., Leicester, United Kingdom.
AUTHOR: Gescher, Andreas (correspondence)
CORPORATE SOURCE: Medical Res. Council Toxicology Unit, Centre Mechanisms of Human Toxicity, University of Leicester, Lancaster Road, Leicester LE1 9HN, United Kingdom.
SOURCE: Critical Reviews in Oncology/Hematology, (May 2000) Vol. 34, No. 2, pp. 127-135.
Refs: 62
ISSN: 1040-8428 CODEN: CCRHEC
PUBLISHER IDENT.: S 1040-8428(00)00058-5
COUNTRY: Ireland
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 May 2000
Last Updated on STN: 18 May 2000
AB This review summarises the evidence for the potential antineoplastic activity of the staurosporine analogues 7-hydroxystaurospine (UCN-01) and N-benzoylstaurosporine (CGP 41251) and defines the role of the enzyme family protein kinase C (PKC) in the mechanisms by which these agents interfere with malignant cell growth. PKC function is altered in some neoplasias, and this dysfunction has been related to uncontrolled proliferation. PKC also influences resistance of cancer cells against cytotoxic drugs. Staurosporine analogues compete with ATP, even though the exact action by which they inhibit PKC is more complicated. Staurosporine analogues do not exhibit specificity for particular PKC isoenzymes, but they inhibit 'conventional' PKC isoenzymes more potently than 'novel' and 'atypical' ones. They also interfere directly with the cell cycle machinery. Both CGP 41251 and UCN-01 are currently progressing through clinical evaluation. There is a remarkable difference in pharmacokinetic handling of CGP 41251 and UCN-01 between rodents and humans. CGP 41251 and UCN-01 might offer advantages in cancer therapy when applied in combination with conventional cytotoxic agents. Copyright (C) 2000 Elsevier Science Ireland Ltd.

L14 ANSWER 21 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2000:459468 HCAPLUS Full-text
DOCUMENT NUMBER: 133:202432
TITLE: PKC412-a protein kinase inhibitor with a broad therapeutic potential
AUTHOR(S): Fabbro, Doriano; Ruetz, Stephan; Bodis, Stephan; Pruschy, Martin; Csermak, Katalin; Man, Anthony; Campochiaro, Peter; Wood, Jeanette; O'Reilly, Terence;

Meyer, Thomas
CORPORATE SOURCE: Department of Oncology Research and Clinical Oncology, Novartis Pharma Inc., Basel, CH-4002, Switz.
SOURCE: Anti-Cancer Drug Design (2000), 15(1), 17-28
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with many refs. The staurosporine derivative PKC412 was originally identified as an inhibitor of protein kinase C (PKC) and subsequently shown to inhibit other kinases including the kinase insert domain receptor (KDR) (vascular endothelial growth factor receptor, VEGF-R2), the receptor of platelet-derived growth factor, and the receptor for the stem cell factor, c-kit. PKC412 showed a broad antiproliferative activity against various tumor and normal cell lines in vitro, and was able to reverse the Pgp-mediated multidrug resistance of tumor cells in vitro. Exposure of cells to PKC412 resulted in a dose-dependent increase in the G2/M phase of the cell cycle concomitant with increased polyploidy, apoptosis and enhanced sensitivity to ionizing radiation. PKC412 displayed a potent antitumor activity as single agent and was able to potentiate the antitumor activity of some of the clin. used cytotoxins (Taxol and doxorubicin) in vivo. The combined treatment of PKC412 with loco-regional ionizing irradiation showed significant antitumor activity against tumors which are resistant to both ionizing radiation and chemotherapeutic agents (dysfunctional p53). The finding that PKC412 is an inhibitor of the VEGF-mediated cellular signaling via inhibition of KDR and PKC in vitro is consistent with the in vivo inhibition of VEGF-dependent angiogenesis in a growth factor implant model. Orally administered PKC412 also strongly inhibited retinal neovascularization as well as laser-induced choroidal neovascularization in murine models. In summary PKC412 may suppress tumor growth by inhibiting tumor angiogenesis in addition to directly inhibiting tumor cell proliferation via its effects on PKC and/or other protein kinases. PKC412 is currently in Phase I clin. trials for treatment of advanced cancer as well as for the treatment of ischemic retinopathy.
REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 22 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 1999:116076 HCAPLUS Full-text
DOCUMENT NUMBER: 130:346942
TITLE: A high throughput system for the evaluation of protein kinase C inhibitors based on Elk1 transcriptional activation in human astrocytoma cells
AUTHOR(S): Sharif, Taraneh R.; Sharif, Mohammed
CORPORATE SOURCE: Department of Molecular Pharmacology, St. Jude Children's Research Hospital, TN, 38105, USA
SOURCE: International Journal of Oncology (1999), 14(2), 327-335
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protein kinase C (PKC) designates a family of kinases that regulate many essential functions including cell growth and differentiation. The tight regulation of PKC activity is crucial for maintaining normal cellular proliferation and excessive activity leads to abnormal or uncontrolled cell growth. Recent reports indicate that malignant glioma cell lines express 100 to 1000-fold higher PKC activity when compared to non-neoplastic astrocytes. This high activity correlates well with the proliferation of tumor cells in vitro. We recently reported on the anti-proliferative properties of selective PKC inhibitors on the growth of U-373MG human astrocytoma cell line, and their

ability to block mitogen-activated protein (MAP) kinase pathway activated by substance P (SP) neuropeptide receptor signaling via a PKC-dependent mechanism. Therefore, inhibiting PKC activity by selective PKC inhibitors may present a promising approach for improving astroglial brain tumor therapy. For this purpose, we constructed a high throughput model cell system to evaluate the efficacy of PKC inhibitors. This system is based on the measurement of light production in U-373MG cells stably transfected with the luciferase reporter gene whose expression depends on the transcriptional activation of GAL4-Elk1 fusion protein by enzyme components of the MAP kinase pathway and the upstream activation of PKC (PKC activation→MAP kinases→GAL4-Elk1 phosphorylation→luciferase expression→luciferase activity). In brief, we have demonstrated that the PKC activator 12-O-tetradecanoyl phorbol 13-acetate (TPA)-induced luciferase activity in this cell system is mediated via the MAP kinase pathway and can be blocked in the presence of MEK1 selective inhibitors (PD 098059 or U0126). We also demonstrated that TPA-induced luciferase activity in U-373MG stable clones can be blocked by PKC inhibitors (CGP 41251, Go 6976, and GF 109203X) in a concentration dependent manner. In contrast, epidermal growth factor (EGF)-induced luciferase activity, which is independent of PKC activation (Ras→Raf-1→MEK1→MAP kinases→GAL4-Elk1 phosphorylation→luciferase expression→luciferase activity), can only be blocked using a selective EGF receptor inhibitor (AG 1478). In conclusion, we have constructed a model cell system for the high throughput screening and identification of PKC inhibitors potentially active against astrocytoma cells in culture.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 23 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 1999:397268 HCAPLUS Full-text
DOCUMENT NUMBER: 131:179168
TITLE: Inhibitors of protein kinases: CGP 41251, a protein kinase inhibitor with potential as an anticancer agent
AUTHOR(S): Fabbro, Doriano; Buchdunger, Elisabeth; Wood, Jeannette; Mestan, Jurgen; Hofmann, Francesco; Ferrari, Stefano; Mett, Helmut; O'Reilly, Terence; Meyer, Thomas
CORPORATE SOURCE: Department of Oncology, Novartis Pharma Inc., Basel, CH-4002, Switz.
SOURCE: Pharmacology & Therapeutics (1999), 82(2-3), 293-301
CODEN: PHTHDT; ISSN: 0163-7258
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with many refs. CGP 41251 was originally identified as an inhibitor of protein kinase C (PKC), inhibiting mainly the conventional PKC subtypes, and subsequently shown to inhibit the vascular endothelial growth factor (VEGF) receptor kinase insert domain-containing receptor, which is involved in angiogenesis. CGP 41251 inhibits reversibly intracellular PKC activity, induction of c-fos and the corresponding activation of the mitogen-activated protein kinase induced by either tumor promoting phorbol esters, platelet-derived growth factor, or basic fibroblast growth factor, but not by the epidermal growth factor. CGP 41251 inhibited the ligand-induced autophosphorylation of the receptors for platelet-derived growth factor, stem cell factor, and VEGF (kinase insert domain-containing receptor) that correlated with the inhibition of the mitogen-activated protein kinase activation, but did not affect the ligand-induced autophosphorylation of the receptors for insulin, insulin-like growth factor-I, or epidermal growth

factor. CGP 41251 showed broad antiproliferative activity against various tumor and normal cell lines in vitro, and is able to reverse the p-glycoprotein-mediated multidrug resistance of tumor cells in vitro. CGP 41251 showed in vivo antitumor activity as single agent and inhibited angiogenesis in vivo. Thus, CGP 41251 may suppress tumor growth by inhibiting tumor angiogenesis (via its effects on the VEGF receptor tyrosine kinases) in addition to directly inhibiting tumor cell proliferation (via its effects on PKCs).

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 24 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:147195 HCAPLUS Full-text
DOCUMENT NUMBER: 128:208893
ORIGINAL REFERENCE NO.: 128:41259a,41262a
TITLE: Methods for prevention of cellular proliferation and restenosis
INVENTOR(S): Prescott, Margaret Forney
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Prescott, Margaret Forney
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9807415	A2	19980226	WO 1997-EP4503	19970818 <--
WO 9807415	A3	19980507		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9742055	A	19980306	AU 1997-42055	19970818 <--
ZA 9707433	A	19980220	ZA 1997-7433	19970819 <--

PRIORITY APPLN. INFO.:
US 1996-24219P P 19960820 <--
US 1996-25072P P 19960830 <--
WO 1997-EP4503 W 19970818 <--

AB Methods for the prevention and treatment of diseases involving cellular proliferation and dysfunctional apoptosis are provided. The methods involve administration of PKC inhibitors and derivs. Addnl., local administration of protein kinase C inhibitors are provided for the treatment of restenosis and cancer therapies.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 25 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 1998:644681 HCAPLUS Full-text
DOCUMENT NUMBER: 130:47200
TITLE: A novel approach for examining the anti-proliferative effect of protein kinase C inhibitors against human astrocytoma cells
AUTHOR(S): Sharif, Taraneh R.; Sharif, Mohammed
CORPORATE SOURCE: Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA

SOURCE: International Journal of Oncology (1998), 13(4), 685-692
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Prognosis for astroglial brain tumors that are not amenable to surgical resection remains poor and even successful treatment with current chemo-radiotherapy is associated with debilitating sequelae. Consequently, a need to identify novel therapeutics for the treatment of brain tumors remains. Regulation of protein kinase C (PKC) whose activity regulates many cellular functions is crucial for maintaining normal cellular proliferation. Recent reports indicate that malignant glioma cell lines express 100 to 1000-fold higher PKC activity when compared to non-neoplastic astrocytes. In this study the authors used a novel approach for the evaluation of known PKC inhibitors (CGP 41251, Go 6976, and tamoxifen) as chemotherapeutic agents for the inhibition of growth of an astroglial derived cell line. For this purpose, the authors constructed a model cell system based on the measurement of light production in cells transfected with the luciferase reporter gene whose expression was quantitated by a highly sensitive, rapid, and easy to perform assay. The authors isolated U-373MG/MEK1c clone whose highly increased luciferase activity was independent of external stimuli and directly proportional to cell number, and therefore, was used as a measure of cell proliferation to quantitate the effects of several PKC inhibitors on growth of astrocytoma cells in vitro. In conclusion, the authors have constructed a novel cell system that can be utilized for high throughput screening and identification of potential anticancer drugs active against astrocytoma cells in culture.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 26 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:86136 HCAPLUS Full-text
DOCUMENT NUMBER: 128:178669
ORIGINAL REFERENCE NO.: 128:35211a,35214a
TITLE: Mitogenic signaling by substance P and bombesin-like neuropeptide receptors in astrocytic/glial brain tumor-derived cell lines (review)
AUTHOR(S): Sharif, Mohammed
CORPORATE SOURCE: Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: International Journal of Oncology (1998), 12(2), 273-286
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 106 refs. Neuropeptides such as substance P (SP) and bombesin regulate many biol. processes through binding to and activating their resp. cell surface receptors. Recently, the authors reported that many astrocytic/glial-derived brain tumor cell lines express functional SP and bombesin receptors (43% and 85%, resp.). Activation of these neuropeptide receptors stimulates several signaling pathways that regulate transcription and translation leading to the induction of mitogenesis in several cell types including astrocytic brain tumor-derived cell lines. The authors have also shown that a number of signaling pathways are induced by SP and/or bombesin receptors in astrocytic/glial-derived brain tumor cell lines and demonstrated that inhibiting these pathways by selective compds. such as PD 098059, tamoxifen, CGP 41251, and rapamycin blocks cell growth. In summary, mitogenic signaling by neuropeptides may play a role in brain tumor growth and/or tumor

progression, and selective compds. capable of blocking mitogenic signaling have potential to be useful in the treatment of brain tumors.
REFERENCE COUNT: 106 THERE ARE 106 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 27 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1998304347 EMBASE Full-text
TITLE: Protein kinase C isoform expression and function in transformed and non-transformed pancreatic acinar cell lines.
AUTHOR: Raffaniello, R.D. (correspondence); Nam, J.; Cho, I.; Lin, J.
CORPORATE SOURCE: Gastrointest. Cell Biol. Laboratory, Department of Medicine, Stt. Univ. New York-Hlth. Sci. C., Brooklyn, NY 11203, United States.
AUTHOR: Bao, L.Y.; Michl, J.
CORPORATE SOURCE: Department of Medicine, Stt. Univ. New York-Hlth. Sci. C., Department of Pathology, Brooklyn, NY 11203, United States.
AUTHOR: Michl, J.
CORPORATE SOURCE: Department of Medicine, Stt. Univ. New York-Hlth. Sci. C., Dept. of Anatomy and Cell Biology, Brooklyn, NY 11203, United States.
AUTHOR: Raufman, J-P.
AUTHOR: Raffaniello, R.D. (correspondence)
CORPORATE SOURCE: Gastrointestinal Cell Biology Lab., State University of New York, Health Science Center at Brooklyn, Brooklyn, NY 11203, United States.
SOURCE: Biochemical and Biophysical Research Communications, (8 May 1998) Vol. 246, No. 1, pp. 166-171.
Refs: 28
ISSN: 0006-291X CODEN: BBRCA9
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 001 Anatomy, Anthropology, Embryology and Histology
029 Clinical and Experimental Biochemistry
048 Gastroenterology
005 General Pathology and Pathological Anatomy
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Sep 1998
Last Updated on STN: 24 Sep 1998

AB Members of the protein kinase C (PKC) family of multifunctional serine/threonine phosphorylating enzymes are believed to play a role in regulating cellular differentiation and proliferation in many cell types. In the present study, we examined the expression of PKC isoforms in non-transformed (BMRPA.430) and transformed (TUG3) rat pancreatic acinar cell lines and compared this to PKC expression in freshly dispersed acini from rat pancreas. BMRPA.430 cells maintain characteristics of normal acini and are not tumorigenic, whereas TUC3 cells do not express tight junctions or polygonal morphology and are tumorigenic. As reported previously, PKC α, δ, ε, and ζ are expressed in freshly prepared acini. Likewise, these isoforms were detected in both the BMRPA.430 and TUC3 cell lines. In addition, PKCθ, a novel isoform, was detected in all three cell types at low levels. We used two PKC inhibitors to examine the role of PKC in acinar cell proliferation. CGP 41 251, a selective PKC inhibitor, and Go 6976, an agent which specifically inhibits calcium-dependent PKC isoforms, inhibited cell

proliferation of both cell lines. Translocation of PKCα to the membrane was not observed in either cell line. Hence, our data indicate that ras-induced transformation does not alter PKC isoform expression in pancreatic acinar cells and that activation of PKCα is involved with acinar cell growth.

L14 ANSWER 28 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 1998:419333 HCAPLUS Full-text
DOCUMENT NUMBER: 129:197639
ORIGINAL REFERENCE NO.: 129:39971a,39974a
TITLE: Reversal of multidrug resistance by the staurosporine derivatives CGP 41251 and CGP 42700
AUTHOR(S): Utz, Irene; Spitaler, Martin; Rybczynska, Maria; Ludescher, Christof; Hilbe, Wolfgang; Regenass, Urs; Grunicke, Hans; Hofmann, Johann
CORPORATE SOURCE: Institute of Medical Chemistry and Biochemistry, University of Innsbruck, Innsbruck, A-6020, Austria
SOURCE: International Journal of Cancer (1998), 77(1), 64-69
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It has been shown previously that the staurosporine derivative CGP 41251, a specific inhibitor of protein kinase C (IC50 = 50 nM), exhibits antitumor activity and reverses mdr1-mediated multidrug resistance. At present, the compound is evaluated as an anticancer drug in clin. phase 1 trials. We compared the effects of CGP 41251 with CGP 42700, another staurosporine derivative, which exhibits low protein kinase C inhibiting activity (IC50 = >100 μM). We found that in contrast to CGP 41251, CGP 42700 does not show antiproliferative activity in HeLa and KB cells in tissue culture (up to a concentration of 10 μM). We compared both compds. for their ability to reverse mdr1-mediated resistance in KB-C1 and in HeLa-MDR1 cells (transfected with the mdr1 gene). CGP 42700 is able to reverse mdr1-mediated resistance to a similar extent as CGP 41251. The intracellular accumulation of rhodamine 123 in KB-C1 cells following pretreatment with CGP 41251 for 30 min was higher than that following treatment with CGP 42700 if determined in medium without serum. However, quantitation of rhodamine efflux in an ex vivo assay using human CD8+ cells in serum showed that CGP 42700 is more effective in inhibiting the efflux of rhodamine 123 than CGP 41251. We conclude from our results that (1) CGP 42700 is more effective in reversal of multidrug resistance in serum than CGP 41251, indicating that the compound may be useful for treatment of patients, and (2) CGP 42700 does not inhibit protein kinase C and cell proliferation and, therefore, may be less toxic and elicit less side effects in humans than other chemosensitizers.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 29 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:617993 HCAPLUS Full-text
DOCUMENT NUMBER: 127:272793
ORIGINAL REFERENCE NO.: 127:53117a,53120a
TITLE: Antiproliferative combinations, containing raf-targeted oligonucleotides and chemotherapeutic compounds
INVENTOR(S): Muller, Marcel; Geiger, Thomas; Altmann, Karl-Heinz; Fabbro, Doriano; Monia, Brett
PATENT ASSIGNEE(S): Novartis AG, Switz.
SOURCE: PCT Int. Appl., 118 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9732604	A1	19970912	WO 1997-EP875	19970224 <--
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9720925	A	19970922	AU 1997-20925	19970224 <--
ZA 9701936	A	19970908	ZA 1997-1936	19970306 <--
PRIORITY APPLN. INFO.:			US 1996-612787 A	19960307 <--
			WO 1997-EP875 W	19970224 <--

AB The invention relates to combinations of raf-targeted (especially c-raf-targeted) deoxyribo- and ribo-oligonucleotides and derivs. thereof with other chemotherapeutic compds., as well as to pharmaceutical prepns. and/or therapies, in relation to disease states which respond to such oligonucleotides or oligonucleotide derivs., especially to modulation of the activity of a regulatory protein. In particular, the invention relates to products or combinations comprising antisense oligonucleotides or oligonucleotide derivs. targeted to nucleic acids encoding raf and other (preferably standard) chemotherapeutics, either in fixed combination or for chronol. staggered or simultaneous administration, and the combined use of both classes of compds., either in fixed combination or for chronol. staggered or simultaneous administration, for the treatment of proliferative diseases, especially tumor diseases, that can be treated by inhibition of raf activity, i.e., where the antisense oligonucleotides or oligonucleotide derivs. are targeted to nucleic acids encoding the regulatory protein raf or active mutated derivs. thereof.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 30 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1997086261 EMBASE Full-text
TITLE: Stimulation by extracellular ATP and UTP of the stress-activated protein kinase cascade in rat renal mesangial cells.
AUTHOR: Huwiler, Andrea
CORPORATE SOURCE: Department of Pharmacology, Biozentrum, University of Basel, Klingelbergstrasse 70, CH-4056 Basel, Switzerland.
AUTHOR: Van Rossum, Gerda; Wartmann, Markus
CORPORATE SOURCE: Ciba-Geigy Ltd., Research Department, Pharmaceuticals Division, CH-4002 Basel, Switzerland.
AUTHOR: Pfeilschifter, Josef (correspondence)
CORPORATE SOURCE: Zentrum der Pharmakologie, Klinkum der Johann Wolfgang Goethe-Universitat, Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany.
AUTHOR: Pfeilschifter, Josef (correspondence)
CORPORATE SOURCE: Zentrum der Pharmakologie, Klinikum Johann Wolfgang Goethe-Univ, Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany.
SOURCE: British Journal of Pharmacology, (1997) Vol. 120, No. 5, pp. 807-812.

Refs: 58
ISSN: 0007-1188 CODEN: BJPCBM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 14 Apr 1997
Last Updated on STN: 14 Apr 1997

AB 1. Extracellular adenosine 5'-triphosphate (ATP) and uridine 5'-triphosphate (UTP) have been shown to activate a nucleotide receptor (P(2U) receptor) in rat mesangial cells that mediates phosphoinositide and phosphatidylcholine hydrolysis by phospholipases C and D, respectively. This is followed by an increased activity of the mitogen-activated protein kinase cascade and cell proliferation. Here we show that ATP and UTP potently stimulate the stress-activated protein kinase pathway and phosphorylation of the transcription factor c-Jun. 2. Both nucleotides stimulated a rapid (within 5 min) and concentration-dependent activation of stress-activated protein kinases as measured by the phosphorylation of c-Jun in a solid phase kinase assay. 3. When added at 100 μM the rank order of potency of a series of nucleotide analogues for stimulation of c-Jun phosphorylation was UTP > ATP = UDP = ATPγS > 2-methylthio-ATP > βγ-imido-ATP = ADP > AMP = UMP = adenosine = uridine. Activation of stress-activated protein kinase activity by ATP and UTP was dose-dependently attenuated by suramin. 4. Down-regulation of protein kinase C-α, -δ and -ε isoenzymes by 24 h treatment of the cells with 12-O-tetradecanoylphorbol 13-acetate did not inhibit ATP- and UTP-induced activation of c-Jun phosphorylation. Furthermore, the specific protein kinase C inhibitors, CGP 41251 and Ro 31-8220, did not inhibit nucleotide-stimulated c-Jun phosphorylation, suggesting that protein kinase C is not involved in ATP- and UTP-triggered stress-activated protein kinase activation. 5. Pretreatment of the cells with pertussis toxin or the tyrosine kinase inhibitor, genistein, strongly attenuated ATP- and UTP-induced c-Jun phosphorylation. Furthermore, N-acetyl-cysteine completely blocked the activation of stress-activated protein kinase in response to extracellular nucleotide stimulation. 6. In summary, these results suggest that ATP and UTP trigger the activation of the stress-activated protein kinase module in mesangial cells by a pathway independent of protein kinase C but requiring a pertussis toxin - sensitive G-protein and tyrosine kinase activation.

L14 ANSWER 31 OF 44 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 7
ACCESSION NUMBER: 1997:162478 BIOSIS Full-text
DOCUMENT NUMBER: PREV199799461681
TITLE: Protein kinase C: A worthwhile target for anticancer drugs?.
AUTHOR(S): Caponigro, Francesco [Reprint author]; French, Raymond C.; Kaye, Stan B.
CORPORATE SOURCE: Divisione Oncologia Medica A, Istituto Nazionale per lo Studio, la Cura dei Tumori 'Fondazione G. Pascale', Via M. Semmola, 80131 Napoli, Italy
SOURCE: Anti-Cancer Drugs, (1997) Vol. 8, No. 1, pp. 26-33.
CODEN: ANTDEV. ISSN: 0959-4973.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Apr 1997

Last Updated on STN: 15 Apr 1997

AB Protein kinase C (PKC) is an enzyme family with serine/threonine kinase function which is involved In the transduction of signals for cell proliferation and differentiation. The Important role played in processes relevant to neoplastic transformation, carcinogenesis and tumor cell invasion renders PKC a potentially suitable target for anticancer therapy. Bryostatin 1, a macrocyclic lactone Isolated from Bugula nerutina, is a partial PKC agonist, and has shown potent antineoplastic properties in vitro and in vivo. Staurosporine, an alkaloid isolated from microbial sources, Is one of the most potent PKC Inhibitors and has shown high antiproliferative activity in vitro, but poor selectivity. Staurosporine analogs have thus been synthesized with the aim of obtaining more selective PKC Inhibition; among these, CGP 41251 has shown reduced PKC inhibitory activity, but a higher degree of selectivity when assayed for inhibition of different kinases. Several studies Indicate a role for PKC in the regulation of the multidrug resistance (MDR) phenotype, since several PKC Inhibitors are able to partially reverse MDR and Inhibit P-glycoprotein (Pgp) phosphorylation. The MDR phenotype is also associated with variation In PKC isoenzyme content, in particular with PKC-alpha overexpression. While adequate PKC modulation might offer an attractive concept to modulate MDR, other potential mechanisms of PKC interaction with anticancer drugs exist and have been documented, such as the enhancement of chemotherapy-induced apoptosis by safingol, a specific PKC Inhibitor. Three phase I clinical trials with bryostatin have been completed so far and have shown that myalgia is the dose-limiting toxicity, while some antitumor activity Is evident. Safingol Is presently undergoing a phase I clinical trial In combination with doxorubicin. While no definitive data are presently available, It appears that safingol plasma levels approach those associated with chemopotentiation in animals and no pharmacokinetic interaction between the two drugs exists. Drugs targeting PKC are well worth considering for clinical trials, particularly for their potential as modulators of currently available cytotoxic agents.

L14 ANSWER 32 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 8

ACCESSION NUMBER:	1996:388875 HCAPLUS Full-text
DOCUMENT NUMBER:	125:48662
ORIGINAL REFERENCE NO.:	125:9081a,9084a
TITLE:	Inhibition of the growth of glioblastomas by CGP 41251, an inhibitor of protein kinase C, and by a phorbol ester tumor promoter
AUTHOR(S):	Begemann, Martin; Kashimawo, Sharafadeen A.; Choi, Yu-jeong A.; Kim, Susan; Christiansen, Kim M.; Duigou, Gregg; Mueller, Marcel; Schieren, Ira; Ghosh, Subrata; et al.
CORPORATE SOURCE:	Columbia-Presbyterian Cancer Center, New York, NY, 10032, USA
SOURCE:	Clinical Cancer Research (1996), 2(6), 1017-1030 CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER:	American Association for Cancer Research
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Protein kinase C (PKC) plays a central role in signal transduction pathways that mediate the action of certain growth factors, tumor promoters, and cellular oncogenes. To explore whether PKC might be an appropriate target for the chemotherapy of human brain tumors, cell lines were established from five glioblastomas, one mixed gliosarcoma and glioblastoma, two astrocytomas, and one choroid plexus carcinoma. The staurosporine derivative CGP 41251, an inhibitor of PKC, inhibited cell proliferation in all nine cell lines with an IC50 in the range of 0.4 μM. Drug withdrawal and clonogenicity assays showed

that CGP 41251 induced an irreversible growth arrest. Three cell lines were examined in detail: two human glioblastoma cell lines, GB-1 and GB-2, and one gliosarcoma cell line, GS-1. All of these three cell lines were highly aneuploid and displayed morphologies and immunohistochem. markers characteristic of the glial lineage. The compound 12-0-tetradecanoylphorbol-13-acetate (TPA), a tumor promoter and activator of PKC, also inhibited the growth of these cell lines. CGP 41251 in combination with TPA caused further growth inhibition. Cultures treated with CGP 41251 displayed an increase in the fraction of cells in G2-M, a decrease of cells in S phase, and no consistent effect on G0-G1. Immunohistochem. analyses demonstrated that growth inhibition by CGP 41251 was associated with the formation of giant nuclei with extensive fragmentation and apoptotic bodies. These effects of CGP 41251 were abrogated by withdrawal of serum from the medium or by exposure of these cells to aphidicolin, actinomycin D, cycloheximide, or TPA. In contrast to the effects seen with the glioblastoma cell lines, nontransformed astrocyte lines remained viable in the presence of 0.4 and 0.8 μM CGP 41251 and displayed only a slight increase in the fraction of giant nuclei with fragmentation. The antitumor activity of CGP 41251 was demonstrated in vivo against xenografts of the glioblastoma cell lines U87 MG and U373 MG. These findings suggest that CGP 41251 might be a useful agent for the treatment of glioblastomas.

L14 ANSWER 33 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 1996:419832 HCAPLUS Full-text
DOCUMENT NUMBER: 125:131843
ORIGINAL REFERENCE NO.: 125:24377a,24380a
TITLE: A strategy for screening anti-tumor drugs utilizing oncogenes encoded in retroviral vectors
AUTHOR(S): Corbley, Michael J.; Cherington, Van; Traxler, Peter M.; Lydon, Nicholas B.; Roberts, Thomas M.
CORPORATE SOURCE: Division Cellular and Molecular Biology, Dana-Farber Cancer Institute, Boston, MA, 02115, USA
SOURCE: International Journal of Cancer (1996), 66(6), 753-759
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A novel strategy for isolating potential anti-tumor drugs is presented. It is predicted on the idea that future anti-tumor drugs will be specific inhibitors of the signal-transduction pathways responsible for cell proliferation. Briefly, retroviral vectors are used to introduce focus-forming oncogenes into a test population to target cells, which are grown to confluence and treated with signal-transduction inhibitors. The inhibitors are screened for the ability to suppress the development of transformed foci without killing the confluent monolayer of nontransformed quiescent cells. For this work, a panel of inhibitors was first screened against the oncogene ras. The protein kinase C (PKC) inhibitor CGP 41251 and the protein tyrosine kinase (PTK) inhibitor CGP 45047 suppressed ras-induced focus formation and left a viable monolayer of quiescent cells. Focus inhibition was reversible; conversely, drug addition to developing foci retarded further expansion. CGP 41251 generally blocked proliferation of ras or control cells, suggesting that oncogenes cannot substitute for PKC. PTK inhibitors erbstatin and CGP 520 and phosphatase inhibitor okadaic acid failed to inhibit focus formation at concns. toxic to the monolayer. Lavendustin A and CGP 47778A showed neither focus inhibition nor toxicity. In the complementary screen, a single inhibitor (CGP 41251) was tested against several oncogenes, including src, raf and polyomavirus middle T antigen. Focus formation by all oncogenes was suppressed. The strategy has several advantages over current drug-screening

assays, and it can be adapted to large-scale screening with many drugs and many oncogenes.

L14 ANSWER 34 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1996234182 EMBASE Full-text
TITLE: Differential modulation of protein kinase C isozymes in rat parotid acinar cells. Relation to amylase secretion.
AUTHOR: Terzian, A.R.; Zhang, X.; Rubin, R.P., Dr. (correspondence)
CORPORATE SOURCE: Dept. of Pharmacology/Toxicology, State University of New York, School of Medicine, Buffalo, NY 14214, United States.
SOURCE: Biochemical Pharmacology, (1996) Vol. 52, No. 4, pp. 569-577.
ISSN: 0006-2952 CODEN: BCPCA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
003 Endocrinology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Sep 1996
Last Updated on STN: 16 Sep 1996

AB We investigated the expression, distribution, and activation parameters of protein kinase C (PKC) isozymes in isolated rat parotid acinar cells. By analyzing cellular extracts by western blot analysis and for isozyme-specific RNA, the Ca(2+)-independent PKC-δ, -ε, and -ζ were detected in the cytosolic, particulate (plasma membrane), and nuclear fractions of unstimulated cells, whereas the Ca(2+)-dependent PKC-α was confined to the cytosolic and particulate fractions. The expressed isozymes showed distinct responses to phorbol 12-myristate 13-acetate (PMA), thymeleatoxin, and cell surface receptor agonists with respect to translocation from cytosol to particulate fraction and nucleus, as well as sensitivity to down-regulation caused by prolonged exposure to PMA (3-20 hr). The marked susceptibility to down-regulation displayed by PKC-α and -δ was accompanied by an enhanced secretory response to norepinephrine as compared with control cells. Further, the selective PKC inhibitors Ro 31-8220 and CGP 41251 also produced a concentration-dependent enhancement of norepinephrine-induced amylase secretion. Our findings suggest that PKC-α or -δ plays a negative modulatory role, rather than an obligatory role, in amylase secretion. Also, the localization and redistribution of PKC-ε and -δ to the nucleus by PKC activators imply that one or both of these isozymes may regulate such processes as cellular proliferation and/or differentiation.

L14 ANSWER 35 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1996115707 EMBASE Full-text
TITLE: Site-related differences in G-protein α subunit expression during adipogenesis in vitro: Possible key role for Gq/11 α in the control of preadipocyte differentiation.
AUTHOR: Denis-Henriot, D.; Lacasa, D.; De Mazancourt, P.; Giudicelli, Y. (correspondence)
CORPORATE SOURCE: Department of Biochemistry, INSERM CJF 94-02, Universite Paris V, F78303 Poissy, France.
AUTHOR: Goldsmith, P.K.

CORPORATE SOURCE: Metabolic Diseases Branch, NIDDK, Bethesda, MD 20892, United States.
AUTHOR: De Mazancourt, P.
CORPORATE SOURCE: Hop. Raymond Poincare, 92380 Garches, France.
AUTHOR: Giudicelli, Y. (correspondence)
CORPORATE SOURCE: Department of Biochemistry, INSERM CJF 94-02, Hopital de Poissy, Universite Paris, F78303 Poissy, France.
SOURCE: Biochemical and Biophysical Research Communications, (18 Mar 1996) Vol. 220, No. 2, pp. 443-448.
Refs: 39
ISSN: 0006-291X CODEN: BBRCA9
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Apr 1996
Last Updated on STN: 30 Apr 1996

AB G protein α subunits were compared by immunoblotting in preadipocytes and adipocytes from rat subcutaneous and epididymal adipose tissue at three steps of adipogenesis. The most striking difference concerned the Gq/11 α subunits whose expression decreased during preadipocyte differentiation in subcutaneous cells while it remained constant in epididymal cells. The PKC inhibitor CGP 41251 increased glycerol 3-phosphate dehydrogenase activity (EC 1.1.1.8), a late marker of differentiation, in epididymal preadipocytes but not in subcutaneous cells. There was no difference in the proliferation capacities between subcutaneous and epididymal preadipocytes: in both cells, CGP 41251 led to the same decrease in [(3)H]thymidine incorporation and, at confluence, the amounts of Gq/11 α subunits were equivalent. No major site-related difference was found in the amounts of Gs and Giα subunits during adipogenesis. Thus, compared to epididymal preadipocytes, the higher capacity of subcutaneous preadipocyte to differentiate seems to be correlated with the decrease in Gq/11 α expression and the decreased Gq/11 mediated PKC activation.

L14 ANSWER 36 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 1996:197943 HCAPLUS Full-text
DOCUMENT NUMBER: 124:278308
ORIGINAL REFERENCE NO.: 124:51179a,51182a
TITLE: Effects of the new selective protein kinase C inhibitor 4'-N-benzoylstaurosporine on cell cycle distribution and growth inhibition in human small cell lung cancer cells
AUTHOR(S): Ikegami, Yuri; Yano, Seiichi; Nakao, Kenzo
CORPORATE SOURCE: Drug Discovery Research Unit, Ciba-Geigy Japan Ltd., Takarazuka, 665, Japan
SOURCE: Arzneimittel-Forschung (1996), 46(2), 201-4
CODEN: ARZNAD; ISSN: 0004-4172
PUBLISHER: Cantor
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CGP 41251 (4'-N-benzoylstaurosporine, CAS 120685-11-2) exerts increased selectivity for Ca2+- and phospholipid-dependent protein kinase C inhibition. In this study, the effects of CGP 41251 on cell cycle distribution and growth inhibition were examined in SBC3 human small cell lung cancer (SCLC) cell line. CGP 41251 caused the inhibition of cell proliferation and at 1.0 μmol/l showed almost complete effect. In early S phase synchronized SBC3 cells, CGP 41251 at 1.0 μmol/l did not inhibit an initial progression from early S to G2

phase, but it blocked a process from G2/M to G1 phase completely. After removal of nocodazole block, CGP 41251 at 1.0 μmol/l caused DNA re-replication and induction of polyploidy. In nude mice xenograft, CGP 41251 at a dose of 200 mg/kg showed statistically significant inhibition against this tumor with a T/C value of 21.4%. Histopathol., expansion of central necrosis was observed by the administration of CGP 41251. These results in SBC3 cells indicated that CGP 41251 showed antitumor activity through the inhibition of cell cycle progression from G2/M to G1 phase, and through induction of cells with higher DNA content.

L14 ANSWER 37 OF 44 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 1996250286 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8963653
TITLE: Signal transduction for proliferation of glioma cells in vitro occurs predominantly through a protein kinase C-mediated pathway.
AUTHOR: Baltuch G H; Yong V W
CORPORATE SOURCE: Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Quebec, Canada.
SOURCE: Brain research, (1996 Feb 26) Vol. 710, No. 1-2, pp. 143-9.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 6 Feb 1998
Entered Medline: 5 Dec 1996

AB Previous work has demonstrated that glioma cells have very high protein kinase C (PKC) enzyme activity when compared to non-malignant glia, and that their PKC activity correlates with their proliferation rate. The purpose of this study was to determine whether the elevated PKC activity in glioma is secondary to an autonomously active PKC isoform implying oncogenic transformation, or whether this activity is driven by upstream ligand-receptor tyrosine kinase interactions. We treated established human glioma cell lines A172, U563 or U251 with either the highly selective PKC inhibitor CGP 41 251, or with genistein, a tyrosine kinase inhibitor. The proliferation rate and PKC activity of all the glioma lines was reduced by CGP 41 251; the IC50 values for inhibiting cell proliferation corresponded to the IC50v values for inhibition of PKC activity. Genistein also inhibited cell proliferation, with IC50 proliferation values approximating those for inhibition of tyrosine kinase activity in cell free protein extracts. Importantly, in genistein-treated cells, downstream PKC enzyme activity was dose dependently reduced such that the correlation coefficient for effects of genistein on proliferation rate and PKC activity was 0.92. These findings suggest that upstream tyrosine kinase linked events, rather than an autonomously functioning PKC, result in the high PKC activity observed in glioma. Finally, fetal calf serum (FCS) evoked a strong mitogenic effect on glioma cell lines. This mitogenic activity was completely blocked by CGP 41 251, suggesting that although the many mitogens in FCS for glioma cells signal initially through genistein-inhibitable tyrosine kinases, they ultimately channel through a PKC-dependent pathway. We conclude that proliferative signal transduction in glioma cells occurs through a predominantly PKC-dependent pathway and that selectively targeting this enzyme provides an approach to glioma therapy.

L14 ANSWER 38 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1996053040 EMBASE Full-text
TITLE: Antitumor effect of CGP41251, a new selective protein kinase C inhibitor, on human non-small cell lung cancer cells.
AUTHOR: Ikegami, Yuri (correspondence); Yano, Seiichi; Nakao, Kenzo
CORPORATE SOURCE: Drug Discovery Research Unit, Pharmaceutical Division, Ciba-Geigy Japan Ltd, 10-66, Miyuki-cho, Takarazuka 665, Japan.
SOURCE: Japanese Journal of Pharmacology, (1996) Vol. 70, No. 1, pp. 65-72.
Refs: 26
ISSN: 0021-5198 CODEN: JJPAAZ
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 Feb 1996
Last Updated on STN: 26 Feb 1996

AB The antitumor effect of CGP41251 (4'-N-benzoyl staurosporine), a selective protein kinase C (PKC) inhibitor, was examined on two kinds of human non-small cell lung cancer (NSCLC) cell lines (adenocarcinoma: A549 and squamous cell carcinoma: NCI-H520). CGP41251 at 0.5 or 1.0 μM inhibited the proliferation of these tumor cell lines significantly; However, at 0.1 μM, it did not show any significant inhibition. Cell cycle analysis indicated that CGP41251 at 0.5 or 1.0 μM arrested the cell cycle progression at the G(2)/M phase up to 24 hr, but 0.1 μM did not. It seems that the antiproliferative action of CGP41251 against human NSCLC is related to G(2)/M accumulation. In NCI-H520, CGP41251 caused DNA re-replication without mitosis. In a nude mice xenograft, CGP41251 at a dose of 200 mg/kg showed antitumor activity against these cell lines. Histopathologically, expansion of central necrosis was observed, although no destruction of tumor nests was seen by CGP41251 administration. In both tumor tissues, the PKC activity of the particulate fraction was significantly decreased by CGP41251 treatment. From these results, it is thought that the antitumor activity of CGP41251 against human NSCLS is accompanied by the decrease of PKC activity in the particulate fraction. Moreover, the G(2)/M arrest of the cell cycle induced by CGP41251 might be important for the growth inhibitory action of this compound.

L14 ANSWER 39 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1995137822 EMBASE Full-text
TITLE: Comparison of ability of protein kinase C inhibitors to arrest cell growth and to alter cellular protein kinase C localisation.
AUTHOR: Courage, C.; Budworth, J.; Gescher, A. (correspondence)
CORPORATE SOURCE: Med. Res. Council Toxicology Unit, Center Mechanisms of Human Toxicity, University of Leicester, Lancaster Road, Leicester LE1 9HN, United Kingdom.
SOURCE: British Journal of Cancer, (1995) Vol. 71, No. 4, pp. 697-704.
ISSN: 0007-0920 CODEN: BJCAAI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 23 May 1995
Last Updated on STN: 23 May 1995

AB Inhibitors of protein kinase C (PKC) such as the staurosporine analogues UCN-01 and CGP 41251 possess antineoplastic properties, but the mechanism of their cytostatic action is not understood. We tested the hypothesis that the ability of these compounds to arrest growth is intrinsically linked with their propensity to inhibit PKC. Compounds with varying degrees of potency and specificity for PKC were investigated in A549 and MCF-7 carcinoma cells. When the log values of drug concentration which arrested cell growth by 50% (IC(50)) were plotted against the logs of the IC(50), values for inhibition of cytosolic PKC activity, two groups of compound could be distinguished. The group which comprised the more potent inhibitors of enzyme activity (calphostin C, staurosporine and its analogues UCN-01, RO 31-8220, CGP 41251) were the stronger growth inhibitors, whereas the weaker enzyme inhibitors (trimethylsphingosine, miltefosine, NPC-15437, H-7, H-7I) affected proliferation less potently. GF 109203X was exceptional in that it inhibited PKC with an IC(50) in the 10(-8) M range, yet was only weakly cytostatic. To substantiate the role of PKC in the growth inhibition caused by these agents, cells were depleted of PKC by incubation with bryostatin 1 (1 μM). The susceptibility of these enzyme-depleted cells towards growth arrest induced by staurosporine, RO 31-8220, UCN-01 or H-7 was studied. The drug concentrations which inhibited incorporation of [(3)H]thymidine into PKC-depleted A549 cells by 50% were slightly, but not significantly, lower than those observed in control cells. These results suggest that PKC is unlikely to play a direct role in the arrest of the growth of A549 and MCF-7 cells mediated by these agents. Staurosporine is not only a strong inhibitor of PKC but also mimics activators of this enzyme in that it elicits the cellular redistribution of certain PKC isoenzymes. The ability of kinase inhibitors other than staurosporine to exert a similar effect was investigated. Calphostin C, H-7, H-7I, miltefosine, staurosporine, UCN-01, RO 31-8220, CGP 41251 or GF 109203X were incubated for 30 min with A549 cells in the absence or presence of the PKC activator 12-O-tetradecanoyl phorbol-13-acetate. The subcellular distribution of PKC-α, -ε and -ξ was measured by Western blot analysis. None of the agents affected PKC-α or -ξ. UCN-01, RO 31-8220 and GF 109203X (0.1-1 μM) mimicked staurosporine by causing the cellular translocation of PKC-ε, whereas calphostin C, CGP 41251, H-7, H-7I or miltefosine did not alter the cellular localisation of this PKC isoenzyme. According to these results, translocation of certain PKC isoenzymes is not only a consequence of PKC activation but, in the case of selected staurosporine analogues, also of PKC inhibition.

L14 ANSWER 40 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1994365136 EMBASE Full-text
TITLE: Stimulation by extracellular ATP and UTP of the mitogen-activated protein kinase cascade and proliferation of rat renal mesangial cells.
AUTHOR: Huwiler, A.; Pfeilschifter, J. (correspondence)
CORPORATE SOURCE: Department of Pharmacology, Biozentrum, University of Basel, Klingelbergstrasse 70, CH-4056 Basel, Switzerland.
SOURCE: British Journal of Pharmacology, (1994) Vol. 113, No. 4, pp. 1455-1463.
ISSN: 0007-1188 CODEN: BJPCBM

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 028 Urology and Nephrology
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Dec 1994
Last Updated on STN: 29 Dec 1994

AB Extracellular ATP and UTP have been reported to activate a nucleotide receptor that mediates phosphoinositide and phosphatidylcholine hydrolysis by phospholipases C and D, respectively. Here we report that ATP and UTP potently stimulate mesangial cell proliferation. Both nucleotides stimulate phosphorylation and activation of mitogen-activated protein kinase and a biphasic phosphorylation of the up-stream mitogen-activated protein kinase kinase. When added at 100 μM, ATPγS, UTP and ATP were the most potent activators of mitogen-activated protein kinase. βγ-imido-ATP was somewhat less active and ADP and 2-methylthio-ATP caused a weak induction of enzyme activity. Activation of mitogen-activated protein kinase by both ATP and UTP is dose-dependently attenuated by the P(2)-receptor antagonist, suramin. The protein kinase C activator 12-0-tetradecanoylphorbol 13-acetate, but not the biologically inactive 4α-phorbol 12,13-didecanoate, increased mitogen-activated protein kinase activity in mesangial cells, suggesting that protein kinase C may mediate nucleotide-induced stimulation of mitogen-activated protein kinase. Down-regulation of protein kinase C-α and -δ isoenzymes by 4 h or 8 h treatment with phorbol ester partially inhibited ATP- and UTP-triggered mitogen-activated protein kinase activation. Moreover, a 24 h treatment of mesangial cells with phorbol ester, a regimen that also causes depletion of protein kinase C-ε did not further reduce the level of mitogen-activated protein kinase stimulation. The specific protein kinase C inhibitor, CGP 41251, which displayed a selectivity for the Ca(2+)-dependent isoenzymes, as compared to the Ca(2+)-independent isoenzymes did not inhibit nucleotide-stimulated mitogen-activated protein kinase phosphorylation, thus implicating the involvement of a Ca(2+)-independent protein kinase C isoform. In summary, these results suggest that ATP and UTP trigger the activation of the mitogen-activated protein kinase signalling cascade in mesangial cells and this may be responsible for the potent mitogenic activity of both nucleotides.

L14 ANSWER 41 OF 44 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1995021032 EMBASE Full-text
TITLE: Protein kinase C regulates calmodulin expression in NRK cells activated to proliferate from quiescence.
AUTHOR: Bosch, M.; Lopez-Girona, A.; Bachs, O.; Agell, N., Dr. (correspondence)
CORPORATE SOURCE: Departament de Biologia Cellular, Facultat de Medicina, Universitat de Barcelona, Casanova 143, 08036-Barcelona, Spain.
SOURCE: Cell Calcium, (1994) Vol. 16, No. 6, pp. 446-454.
ISSN: 0143-4160 CODEN: CECADV
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 001 Anatomy, Anthropology, Embryology and Histology
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 1 Feb 1995
Last Updated on STN: 1 Feb 1995

AB We have investigated the levels of calmodulin protein and calmodulin mRNA species during proliferative activation of NRK cells. Cells activated to proliferate from quiescence started to replicate DNA at 15 h, reaching a maximum at 20 h after serum addition. The maximum of mitosis was observed at 24 h. Quiescent cells showed a calmodulin concentration of 1.5 ng/μg of protein. At 10 h after serum addition the amount of calmodulin started to increase, reaching values of 3.0 ng/μg of protein at 24 h. NRK cells expressed predominantly 3 species of calmodulin transcripts: the 1.7 kb from CaM I, the 1.4 kb from CaM II and the 2.3 kb from CaM III. The amount of all the 3 transcripts was low in quiescent cells and 10 h after activation the levels were already high, reaching a maximum around 20 h. At the latter time the amount of the 3 calmodulin mRNAs was 5-10-fold higher than in serum starved cells. Run-on experiments showed that at 20 h after activation the transcription rates of the 3 calmodulin genes were higher than in quiescent cells. The addition of protein kinase C inhibitors to the cultures blocked the increase of the calmodulin transcripts while inhibitors of protein kinase A did not have any effect. Moreover, the addition of submitogenic doses of phorbol 12-tetradecanoate induced the increase of all 3 calmodulin transcripts. These results indicate that protein kinase C regulates calmodulin expression when NRK cells are activated to proliferate.

L14 ANSWER 42 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 12
ACCESSION NUMBER: 1994:499218 HCAPLUS Full-text
DOCUMENT NUMBER: 121:99218
ORIGINAL REFERENCE NO.: 121:17575a,17578a
TITLE: The protein kinase C inhibitor CGP 41251, a staurosporine derivative with antitumor activity, reverses multidrug resistance
AUTHOR(S): Utz, Irene; Hofer, Susanne; Regenass, Urs; Hilbe, Wolfgang; Thaler, Josef; Grunicke, Hans; Hofmann, Johann
CORPORATE SOURCE: Inst. Med. Chem. and Biochem., Univ. Innsbruck, Innsbruck, A-6020, Austria
SOURCE: International Journal of Cancer (1994), 57(1), 104-10
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Multidrug resistance (MDR) is frequently associated with overexpression of a 170-kDa P-glycoprotein (Pgp). Data suggest altered protein kinase C (PKC) activity in cells expressing the multidrug-resistant phenotype. The staurosporine derivative CGP 41251, an exptl. anticancer drug, has been shown to exert selectivity for inhibition of protein kinase C activity and to exhibit antitumor activity in vitro and in vivo. Here the authors show that CGP 41251 is also able to reverse MDR. After treatment of the multidrug-resistant human lymphoblastoid cell line CCRF-VCR1000 with 500 nM Adriamycin, cell proliferation was reduced to 81% of untreated controls. A combination of 500 nM Adriamycin with a non-toxic concentration of 150 nM CGP 41251 (IC50 for inhibition of cell proliferation 420 nM CGP 41251) inhibits cell proliferation of CCRF-VCR1000 cells to 29% of untreated controls. In sensitive CCRF-CEM cells no enhancement of Adriamycin-induced cytotoxicity was observed upon addition of 150 nM CGP 41251. Strong synergism of the inhibition of cell proliferation was also observed after concomitant treatment of KB-8511 cells with CGP 41251 and Vinblastine or Adriamycin. Drug-sensitive KB-31 cells could not be further sensitized to Adriamycin or Vinblastine with CGP 41251 doses above 100 nM. Pretreatment with 50-1000 nM CGP 41251 for 30 min led to a dose-dependent increase in the intracellular accumulation of rhodamine 123,

a substrate of P-glycoprotein. Treatment of multidrug-resistant CCRF-VCR1000 cells with CGP 41251 for 10 min was sufficient to inhibit the efflux of rhodamine 123. Preincubation with CGP 41251 for 12 or 24 h did not alter multidrug resistance gene (mdrI)-mRNA levels. CGP 41251, a drug with antitumor efficacy in exptl. systems, might offer an attractive combination partner for the treatment of tumors expressing the MDR phenotype.

L14 ANSWER 43 OF 44 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 1994:327040 BIOSIS Full-text
DOCUMENT NUMBER: PREV199497340040
TITLE: The protein kinase C inhibitor CGP 41251, a staurosporine derivative with antitumor activity, reverses multidrug resistance.
AUTHOR(S): Utz, Irene [Reprint author]; Hofer, Susanne [Reprint author]; Regenass, Urs; Grunicke, Hans [Reprint author]; Hofmann, Johann [Reprint author]
CORPORATE SOURCE: Inst. Med. Chem. Biochem., Univ. Innsbruck, A-6020 Innsbruck, Austria
SOURCE: Journal of Cellular Biochemistry Supplement, (1994) Vol. 0, No. 18D, pp. 94.
Meeting Info.: Keystone Symposium on Protein Kinase C: Regulation, Structure, Function and Role in Human Disease. Taos, New Mexico, USA. February 26-March 4, 1994.
ISSN: 0733-1959.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 1994
Last Updated on STN: 18 Nov 1994

L14 ANSWER 44 OF 44 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 13

ACCESSION NUMBER: 1993:616957 HCAPLUS Full-text
DOCUMENT NUMBER: 119:216957
ORIGINAL REFERENCE NO.: 119:38397a,38400a
TITLE: Effects of a new protein kinase C inhibitor CGP 41251 on T cell functions: Inhibition of activation, growth, and target cell killing
AUTHOR(S): Alkan, Sefik S.; Rutschmann, Susan; Grogg, Daniel; Erb, Peter
CORPORATE SOURCE: Dep. Allergy/Immunol., Ciba-Geigy Ltd., Basel, CH-4002, Switz.
SOURCE: Cellular Immunology (1993), 150(1), 137-48
CODEN: CLIMB8; ISSN: 0008-8749
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of CGP 41251, a specific inhibitor of protein kinase C (PKC), its inactive derivative CGP 42700, and of staurosporine have been analyzed in vitro on T lymphocyte functions. The proliferation of fresh human peripheral blood lymphocytes stimulated with antigen (PPD) or anti-CD3 mAb was strongly inhibited by both staurosporine (IC50 < 0.01 μM) and CGP 41251 (IC50 = 0.092 μM) but not by the PKC inactive compound CGP 42700 (IC50 > 10 μM). Antigen-specific activation and proliferation of mouse lymph node T cells was inhibited by staurosporine and CGP 41251 with IC50 values of 0.008 and 0.05 μM, resp. The inactive derivative caused 50% inhibition in this mouse T cell assay only at concns. of 25 μM. In order to evaluate possible differential effects of PKC inhibitors on CD4+ T cell subsets, murine T helper cell type 1

(Th1) and type 2 (Th2) clones were used. The KLH-specific clone 9/6 secretes IL-2 and IFN-γ (Th1), whereas clone 9A/B does not secrete these lymphokines but secretes IL-4 and IL-5 (Th2). It was found that CGP 41251 inhibited antigen-induced proliferation of both Th1 and Th2 equally well with an IC50 of 0.02 µM. Furthermore, CGP 41251 inhibited the IL-2 or IL-2 and IL-4-mediated growth of Th1 and Th2 cells (IC50, 0.08 and 0.02 µM, resp.). Moreover, CGP 41251, but not CGP 42700, inhibited antigen-specific killing of target cells by Th1 clones (IC50 = 0.2 µM), a phenomenon which does not require cell proliferation . When Th1 cells were preincubated with the compound, washed, and rested for 24 h, they killed the target cells, whereas killing by similarly preincubated, washed, but not rested Th1 cells was inhibited. Thus, the inhibitory effect of CGP 41251 is reversible and excludes the possibility of inhibition due to toxicity at the IC50 dose given. The comparison of CGP 41251 and staurosporine showed that although CGP 41251 has lower activity, it is more specific and much less toxic than staurosporine. Thus, CGP 41251 is more suitable for PKC studies.

SEARCH HISTORY

```
=> d his ful

     (FILE 'HOME' ENTERED AT 11:41:43 ON 07 MAY 2009)

     FILE 'HCAPLUS' ENTERED AT 11:42:22 ON 07 MAY 2009
                E COUTRE STEVEN/AU
L1           26 SEA ABB=ON  ("COUTRE STEVE"/AU OR "COUTRE STEVEN"/AU OR
                "COUTRE STEVEN E"/AU)
L2            1 SEA ABB=ON  L1 AND ?MIDOSTAURIN?
L3              ANALYZE L2 1 CT :      22 TERMS

     FILE 'REGISTRY' ENTERED AT 11:43:28 ON 07 MAY 2009
L4            1 SEA ABB=ON  MIDOSTAURIN/CN

     FILE 'HCAPLUS' ENTERED AT 11:44:25 ON 07 MAY 2009
L5          358 SEA ABB=ON  L4 OR ?MIDOSTAURIN?
L6           15 SEA ABB=ON  L5 AND (?MASTOCYTO? OR ?MAST?(W)?CELL?(W)?PROLIF?)
L7           47 SEA ABB=ON  L5 AND ?CELL?(W)?PROLIF?
L8            2 SEA ABB=ON  L7 AND (?MASTOCYTO?)
L9           15 SEA ABB=ON  L6 OR L8
L10           1 SEA ABB=ON  L9 AND (PRD<20030618 OR PD<20030618)
L11          19 SEA ABB=ON  L7 AND (PRD<20030618 OR PD<20030618)
L12          20 SEA ABB=ON  L10 OR L11

     FILE 'MEDLINE, BIOSIS, EMBASE, DRUGU' ENTERED AT 11:47:13 ON 07 MAY 2009
L13          50 SEA ABB=ON  L12

     FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 11:50:48 ON 07 MAY 2009
L14          44 DUP REMOV L12 L13 (26 DUPLICATES REMOVED)

     FILE HOME

     FILE HCAPLUS

     Copyright of the articles to which records in this database refer is
     held by the publishers listed in the PUBLISHER (PB) field (available
     for records published or updated in Chemical Abstracts after December
     26, 1996), unless otherwise indicated in the original publications.
     The CA Lexicon is the copyrighted intellectual property of the
     American Chemical Society and is provided to assist you in searching
     databases on STN.  Any dissemination, distribution, copying, or storing
     of this information, without the prior written consent of CAS, is
     strictly prohibited.

     FILE COVERS 1907 - 7 May 2009  VOL 150 ISS 19
     FILE LAST UPDATED: 6 May 2009  (20090506/ED)
     REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Feb 2009
     USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Feb 2009

     HCAplus now includes complete International Patent Classification (IPC)
     reclassification data for the third quarter of 2008.

     CAS Information Use Policies apply and are available at:

     http://www.cas.org/legal/infopolicy.html

     This file contains CAS Registry Numbers for easy and accurate
```

substance identification.

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 5 MAY 2009 HIGHEST RN 1143038-16-7
DICTIONARY FILE UPDATES: 5 MAY 2009 HIGHEST RN 1143038-16-7

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 9, 2009.

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

FILE MEDLINE
FILE LAST UPDATED: 6 May 2009 (20090506/UP). FILE COVERS 1949 TO DATE.

MEDLINE and LMEDLINE have been updated with the 2009 Medical Subject Headings (MeSH) vocabulary and tree numbers from the U.S. National Libra of Medicine (NLM). Additional information is available at

http://www.nlm.nih.gov/pubs/techbull/nd08/nd08_medline_data_changes_2009.

On February 21, 2009, MEDLINE was reloaded. See HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

See HELP RANGE before carrying out any RANGE search.

FILE BIOSIS
FILE COVERS 1926 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1926 TO DATE.

RECORDS LAST ADDED: 6 May 2009 (20090506/ED)

BIOSIS has been augmented with 1.8 million archival records from 1926 through 1968. These records have been re-indexed to match current BIOSIS indexing.

FILE EMBASE
FILE COVERS 1974 TO 7 May 2009 (20090507/ED)

EMBASE was reloaded on March 30, 2008.

EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
 Beginning January 2008, Elsevier will no longer provide EMTREE
 codes as part of the EMTREE thesaurus in EMBASE.  Please update
 your current-awareness alerts (SDIs) if they contain EMTREE
 codes.

 For further assistance, please contact your local helpdesk.

FILE DRUGU
FILE LAST UPDATED: 7 MAY 2009       <20090507/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<
```